

DRAWINGS

Amendments to the Drawings

The attached sheet of formal drawings includes changes to FIGS. 1, 2, 4, 6, 7, 11, 16, 17, 18, 21, 22, 23, 24, 25, 27, 29, 30, 31, 32, 36 and 37. This sheet replaces the original sheet.

The Applicants have submitted formal drawings for FIGS. 1, 2, 4, 6, 7, 11, 17, 21, 25, 30, 31 and 36 that better reveal the structural detail essential for proper understanding of the present invention.

The Applicants have submitted formal drawings for FIGS. 16, 18, 22, 23, 27, 29 that better reveal the structural detail essential for proper understanding of the present invention and have deleted images believed redundant.

The Applicants have provided formal drawings for FIGS. 24, 32 and 37 that have added omitted error bars.

Lastly, the Applicant's have provided formal drawings for FIGS. 3, 5, 8, 9, 10, 12, 13, 14, 15, 19, 20, 26, 28, 33, 34 and 35.

Appendix: Replacement Sheet, Annotated Sheet Showing Changes and Original Sheet.

REMARKS

Amendments to the Specification

The present specification was amended to SEQ ID NOs in order to comply with 37 C.F.R. §§ 1.821-1.825. The Applicants hereby state that the amendments to the specification did not add new subject matter to the specification.

Support for amendments adding SEQ ID NOs to paragraphs ¶¶ 48-52, 79, 81, 113, 140 and 143 can be found throughout the present specification, such as, *e.g.*, Figure 3 and the Sequence Listing.

Support for amendments to paragraphs ¶¶ 72-76, 78, 81, 91-94, 98 and 100 can be found throughout the present specification, such as, *e.g.*, in originally-filed Figures 1-5, 7, 20-23, 27 and 29. Additionally, these same amendments were accepted and entered by the USPTO in parent patent application serial number 10/163,106, filed June 4, 2003 which the present application incorporates by reference in its entirety at ¶ 1.

Amendments to the Claims

Claims 1-44 are pending. The Applicants respectfully ask the Examiner to replace all prior versions and listings of claims in the present application with the listing of claims currently provided. Claims 1-3 were amended; Claims 4-44 were canceled; and Claims 45-52 are new. The Applicants hereby state that the amendments to the claims do not add new subject matter to the specification.

Support for Claims 1-3 can be found throughout the present specification, such as, *e.g.*, ¶ 27; ¶ 38; ¶ 53; ¶ 109; ¶ 125; ¶ 141; ¶ 275; ¶ 277; ¶¶ 284-285; ¶ 288; ¶¶ 291-298; and Example 11.

Support for Claims 45-50 can be found throughout the present specification, such as, *e.g.*, ¶ 27; ¶ 33; ¶ 39; ¶ 53, ¶ 109; ¶ 125; ¶ 288; and Examples 4, 6 and 11.

Support for Claims 51 and 52 can be found throughout the present specification, such as, *e.g.*, ¶ 27; ¶ 33; ¶ 40; ¶ 53; ¶ 109; ¶¶ 111-118; ¶ 125; ¶ 140; ¶ 288; and Examples 4, 6 and 11.

Notice to Comply Pursuant to 37 C.F.R. §§ 1.821-1.825

The Examiner has objected to the Sequence Listing under 37 C.F.R. §§ 1.821-1.825, because each sequence disclosed did not allegedly appear in the Sequence Listing and in the text of the description and claims whenever described.

The Applicant has submitted an amended copy of the computer readable form (CRF) of the Sequence Listing and the written Sequence Listing. The Sequence Listing information recorded in CRF is identical to the written Sequence Listing. The Sequence Listing provided does not contain any new matter as required by 37 C.F.R. §§ 1.821(e), 1.821(f), 1.821(g) and 1.825 (b).

Restriction Requirement under 35 U.S.C. §121

The Examiner has restricted the present application under 35 U.S.C. §121 as allegedly disclosing 9 independent and distinct inventions designated Group I (modified Botulinum neurotoxin type A), Group II (modified Botulinum neurotoxin type B), Group III (modified Botulinum neurotoxin type C1), Group IV (modified Botulinum neurotoxin type C2), Group V (modified Botulinum neurotoxin type D), Group VI (modified Botulinum neurotoxin type E), Group VII (modified Botulinum neurotoxin type F), Group VIII (modified Botulinum neurotoxin type G), Group IX (decreased persistence of Botulinum neurotoxin type A), Group X (decreased persistence of Botulinum neurotoxin type B), Group XI (decreased persistence of Botulinum neurotoxin type C1), Group XII (decreased persistence of Botulinum neurotoxin type C2), Group XIII (decreased persistence of Botulinum neurotoxin type D), Group XIV (decreased persistence of Botulinum neurotoxin type E), Group XV (decreased persistence of Botulinum neurotoxin type F), and Group XVI (decreased persistence of Botulinum

neurotoxin type G). The Applicants elect to prosecute Examiner's Group I (modified Botulinum neurotoxin type A).

CONCLUSION

For the above reasons the Applicants respectfully submit that the claims are in condition for allowance, and the Applicants respectfully urge the Examiner to issue a Notice to that effect. Should there be any questions, the Examiner is invited to call the undersigned agent.

Please use Deposit Account 01-0885 for the payment of any extension of time fees under 37 C.F.R. § 1.136 or any other fees due in connection with the current response.

Respectfully submitted,



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Amdt Date: January 25, 2007
Reply to Jan. 11, 2007 Office Action
Annotated Sheet Showing Changes

FIG. 1.

"GFP-LC/A
(WT)"
and arrow
added

GFP-LC/A (WT)

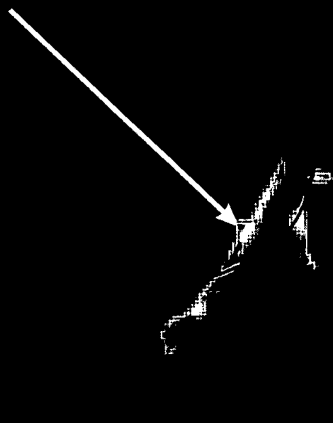
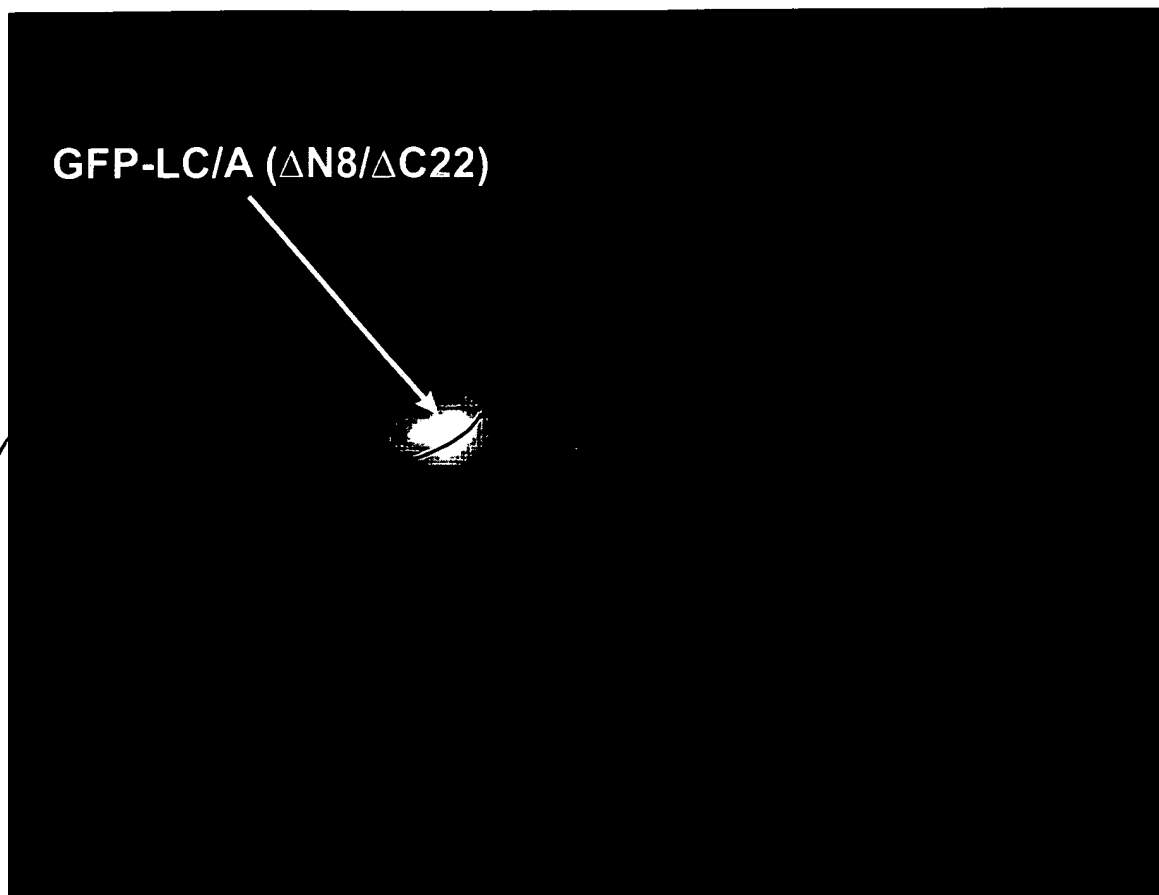


Image quality adjusted and image size enlarged.
Label "GFP-LCA (WT)" deleted
Changed from color to b/w image

FIG. 2.



Label "GFP-LC/A (ΔN8/ΔC22)" and arrow added
Label "GFP-TLCA" deleted
Image in right panel from original Fig. 2 deleted
Image in left panel from original Fig. 2 had image quality adjusted and
image size enlarged and re-oriented.
Changed from color to b/w image.

FIG. 3.

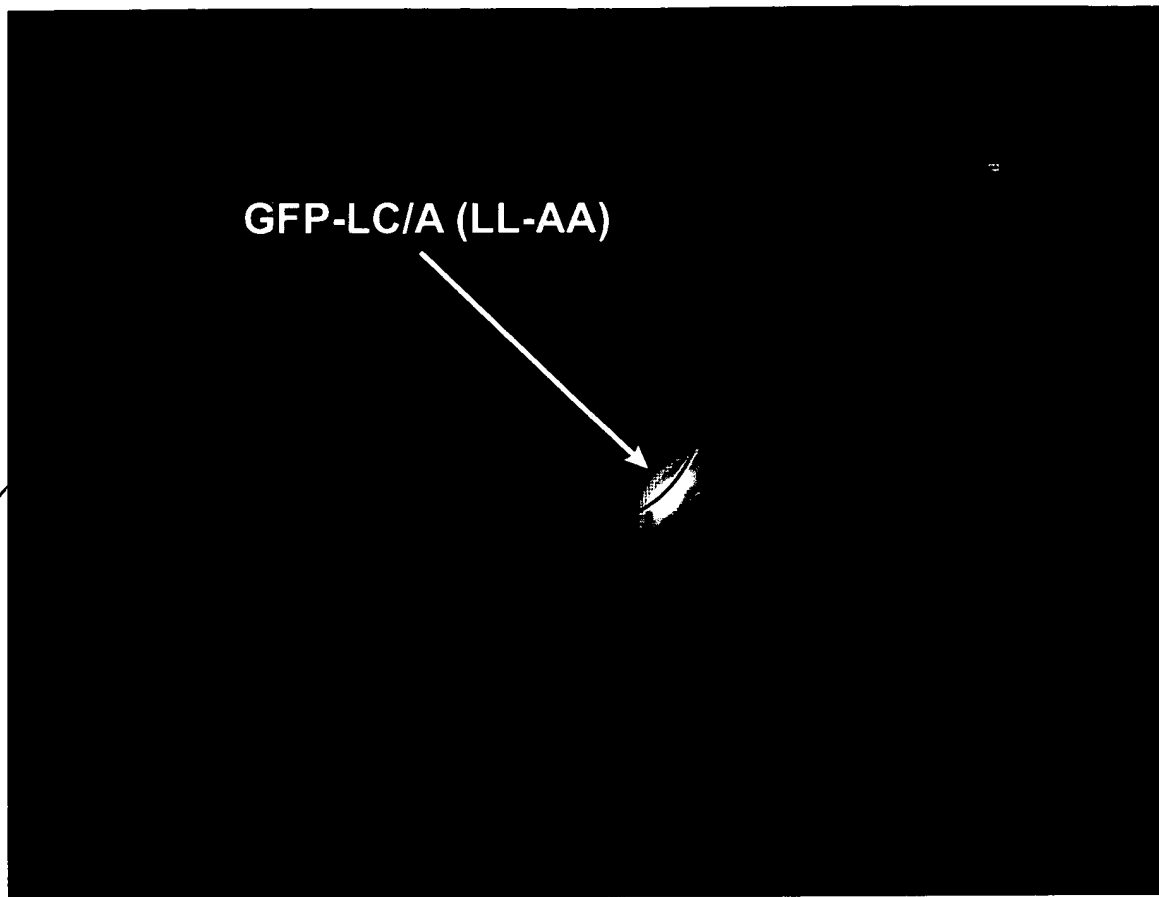
Changed from overline bracket to dotted underline

1 PFVANKQFNFKDPVNGVDIAIYIKIPNAGQMOPVKAFKIHNKIWIPIERDTF
51 TNPEEGDLNPPPEAKQVPVSYYDSTYLSKDNEKDNYLKGVTKLFERIYST
101 DLGRMLLTSIVRGIPIFWGGSTIDTELKVIDTNCINVIQPDGSRSEELNL
151 VIIGPSADIIQFECKSFGHEVLNLTNRNGYGSTQYIRFSPDFTFGFEESLE
201 VDTNPLLGAAGKFAATDPAVTLAHELHAGHRLYGIAINPNRVFKVNTNAYY
251 EMSGLEVSFEELRTFGGHDAKFIDSLQENEFRLYYYNKFKDIASTLNKAK
301 SIVGTTASLOYMKNVFEKEYLLSEDTSGKFSVDKLFDKLYKMLTEIYTE
351 DNFKVFEKVLNRKTYLNFDKAVKINIVPKVNYTIYDGFNLRNTNLAANF
401 NGQNTTEINNMMNFTKLNFTGLFFYKLLCVRGIITTSK
Changed from overline bracket to double underline.

Changed from underline to overline. Label "AN8" added.

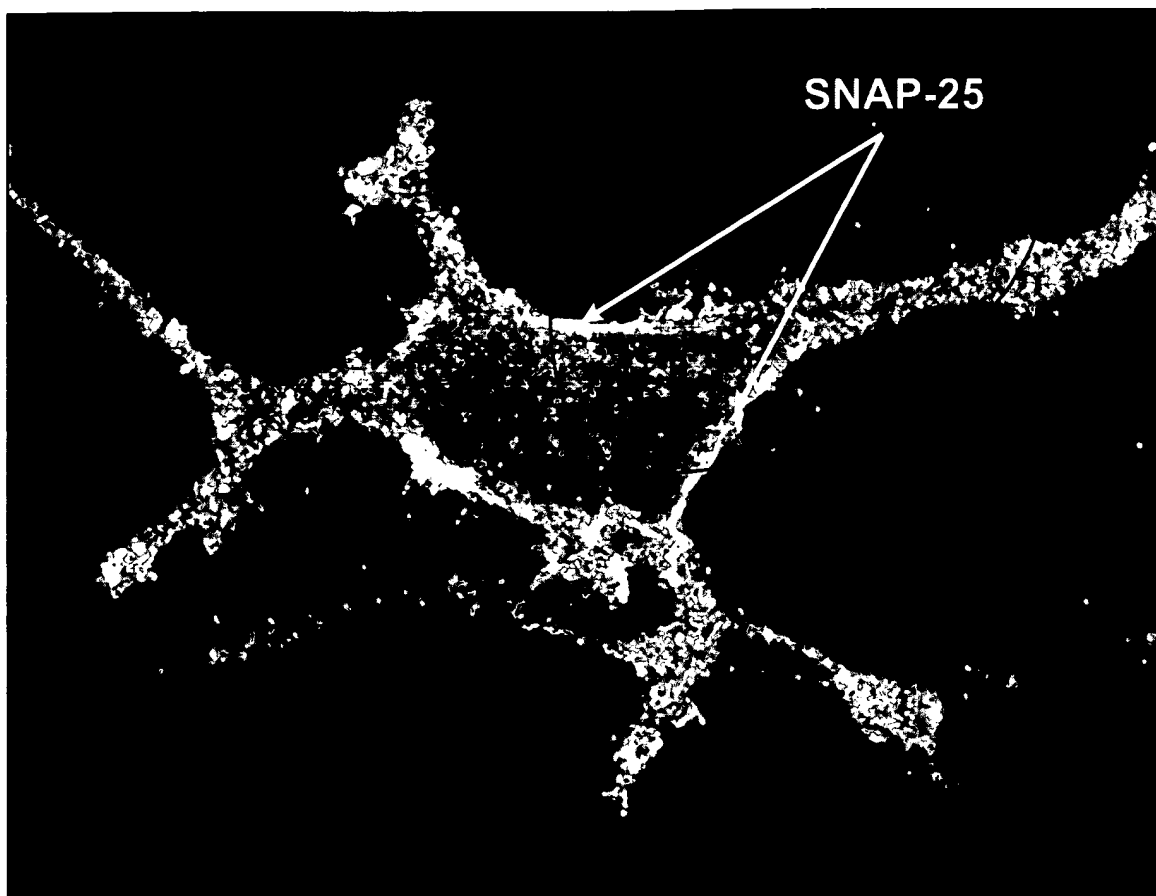
Changed from underline to overline. Label "AC22" added.

FIG. 4.



Label "GFP-LC/A (LL-AA)" and arrow added.
Image quality adjusted and image size enlarged.
Changed from color to b/w image.

FIG. 5.



Label "SNAP-25" deleted
"SNAP-25" and arrow added.
Image quality adjusted and image size enlarged.

FIG. 6.

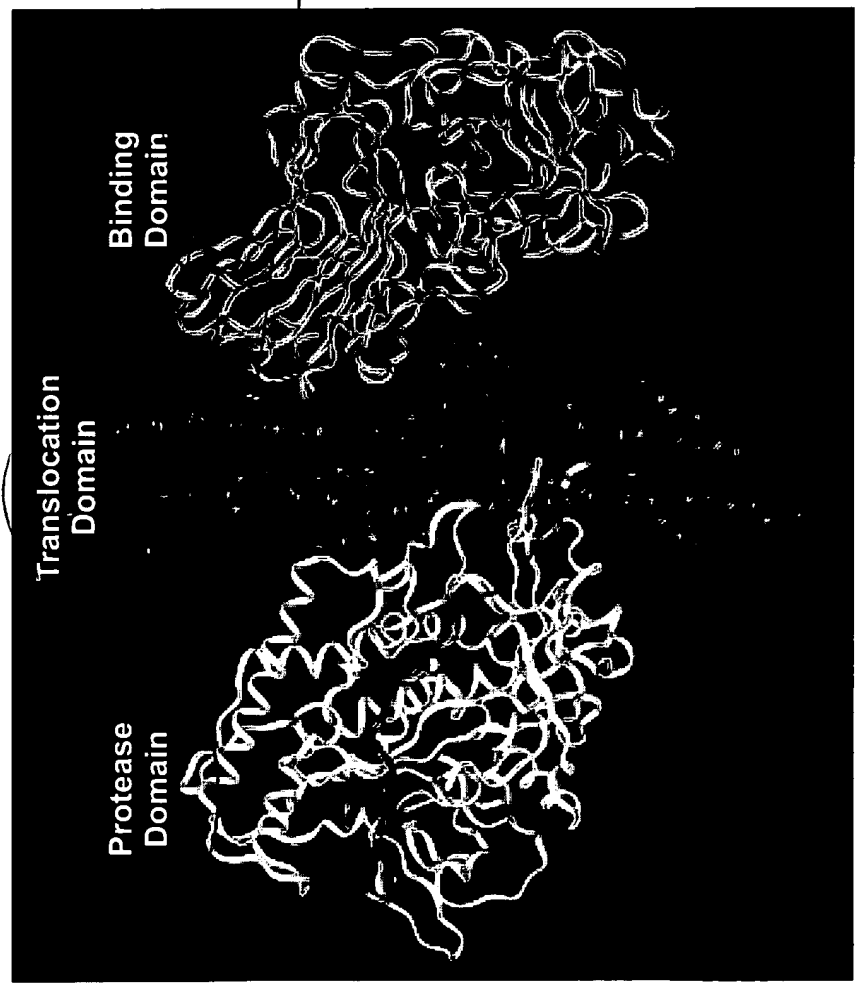
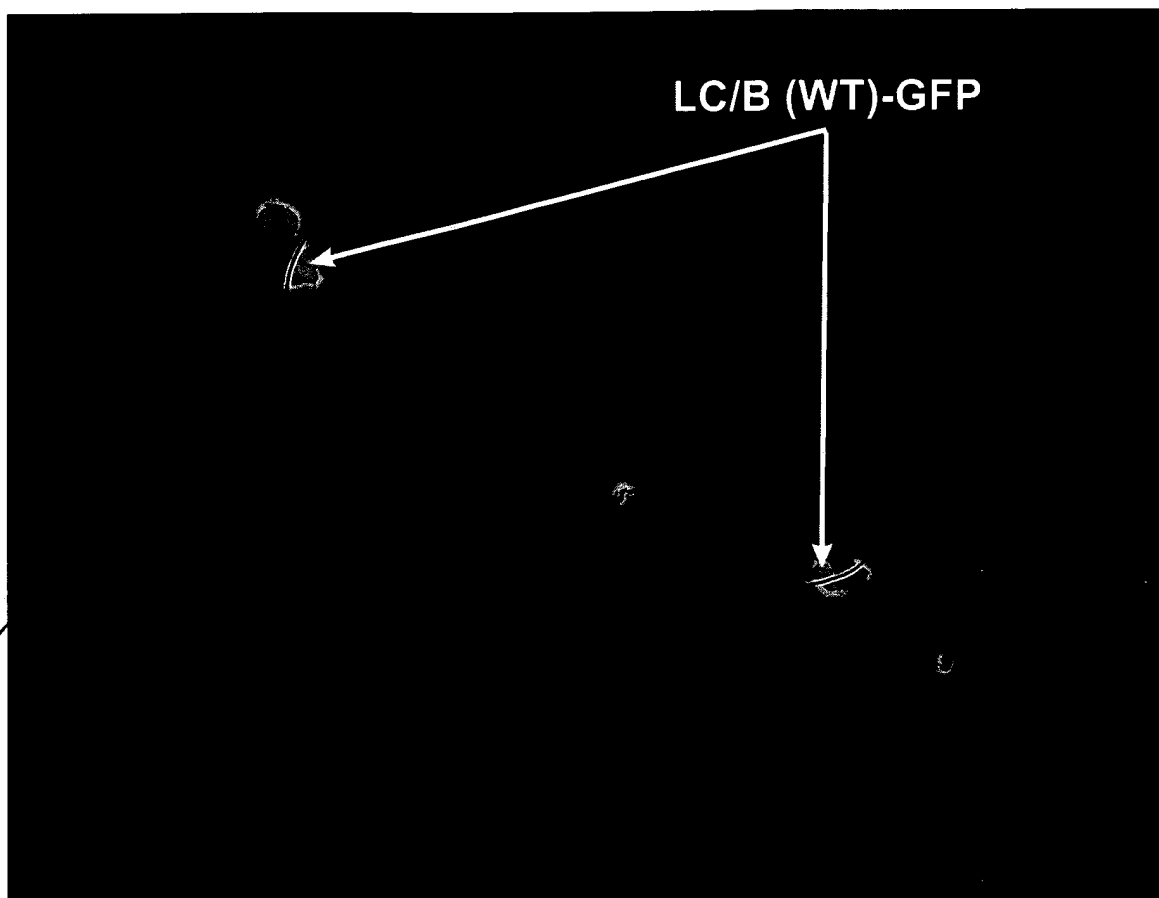


Image quality adjusted and size reduced.
Image changed from color to b/w.
Labeling from original Fig. 6 deleted
Label "Protease Domain," "Translocation Domain," and "Binding Domain" added.

FIG. 7.



Label "GFP-LCB (WT)" deleted

"LC/B (WT)-GFP" added

Image quality adjusted and image size enlarged.

Image changed from color to b/w.

FIG. 8.

1 BoNT/A (Hall A) LC - EFVNKQFNFKDPVNGVDAYIKIPNAGOMQPV-KAFKTHNKIWIPIPERDTFTNPEEGDLNPPPEAKQVPVSYYD 75
BoNT/B (Danish I) LC MPEVTINNENYNDPIDNNNIMMEPPFARGTGRIYKAFKIDRIWIIPERYTTFGYKPEDFNKSSGIFNRDVCEYYD
P NFNYPDI I I P KAFKI KIWIIIPER TF E

76 BoNT/A (Hall A) LC STYLSTDNERNYKGVTKLFEIRIYSTDLGRMLLTSTVRGIPFWGGSTIDTTELKVIDTNCINVIQPDGYSR-SEE 150
BoNT/B (Danish I) LC PDYINTNDKKNIFLOTMIKLFNRJKSKPLGKLEMIINGIPYLGDRRVPLFEFNTNIASVTINKLISNPGEVER
YL T K FL M KLF RI S LG LL II GIPF G I E I V E

151 BoNT/A (Hall A) LC -----LNIVIIIGPSADIIQFECKSFGEVLNLTNRNGYGSTQYIRFSPDFTFGFEESLEFVDNTNPLLGAGKFATDPA 225
BoNT/B (Danish I) LC KKGIFANTIIIFGPGPVLNENETIDIGIQNHFASTRGFGGIMQMKECEPEYVSVENNVQENKASIFNRRGYFSDPA
NLII GP I E G SR GFG IKF PDF F E I F SDPA

226 BoNT/A (Hall A) LC VTTAHELIIHAGHRLYGI AINPNRVFKVNTNAYYEMSGLEVSFEELRTFGGHD AKFTDSLOENEFRLYYNKKFKDI 300
BoNT/B (Danish I) LC LILMHELIIHVLHGLYGIKVD-DLPVNPNEKKFFMQSDAIQAEELTYFGGODPSIITPSTDKSIYDKVLQNERGI
L L HELIH H LYGI I N FF S I EEL TFGG D I D N FK I

301 BoNT/A (Hall A) LC ASTLNKAKSIVG-TTASLOYMKNVFEKEKYLLSEDTSGKFSVDKCLKFDFDKLYKMLTEIYTEDNFVKFFKVLNPKTYL 375
BoNT/B (Danish I) LC VDRLNKVLVCISDPNININIKKFKDKYKFVEDSECKYSIDVESFDKLYKSLMFGFTETNTIAENYKIKTRASYF
LNK I IN KN FKDKY EDS GKFSID FDKLYK L FTE N FKI R SY

376 BoNT/A (Hall A) LC NFDKAVFKIN-IVPKVNTIYDGFNLNNTNLAANFNGQNTETNNMNFTKLNFTGLFEFFYKLLCVRGIITSK 447
BoNT/B (Danish I) LC SDSLPPVKIKNLLDNEIYTIIEGGENISDKDMEKEYRGONKALNKQAYEEIS--KEHLAVYKIQMCKSVK---
KI IL YTI DGFNI L F GQN IN F I YKI K I

Original labels "BoNT-A Italla LC," "BoNT-B Danish I-LC," and "Covsises" deleted.
Labels "BoNT/A (Hall A) LC" and "BoNT/B (Danish I) LC" were added.
Sequence alignment re-drawn to conform wit guidelines.

FIG. 9.

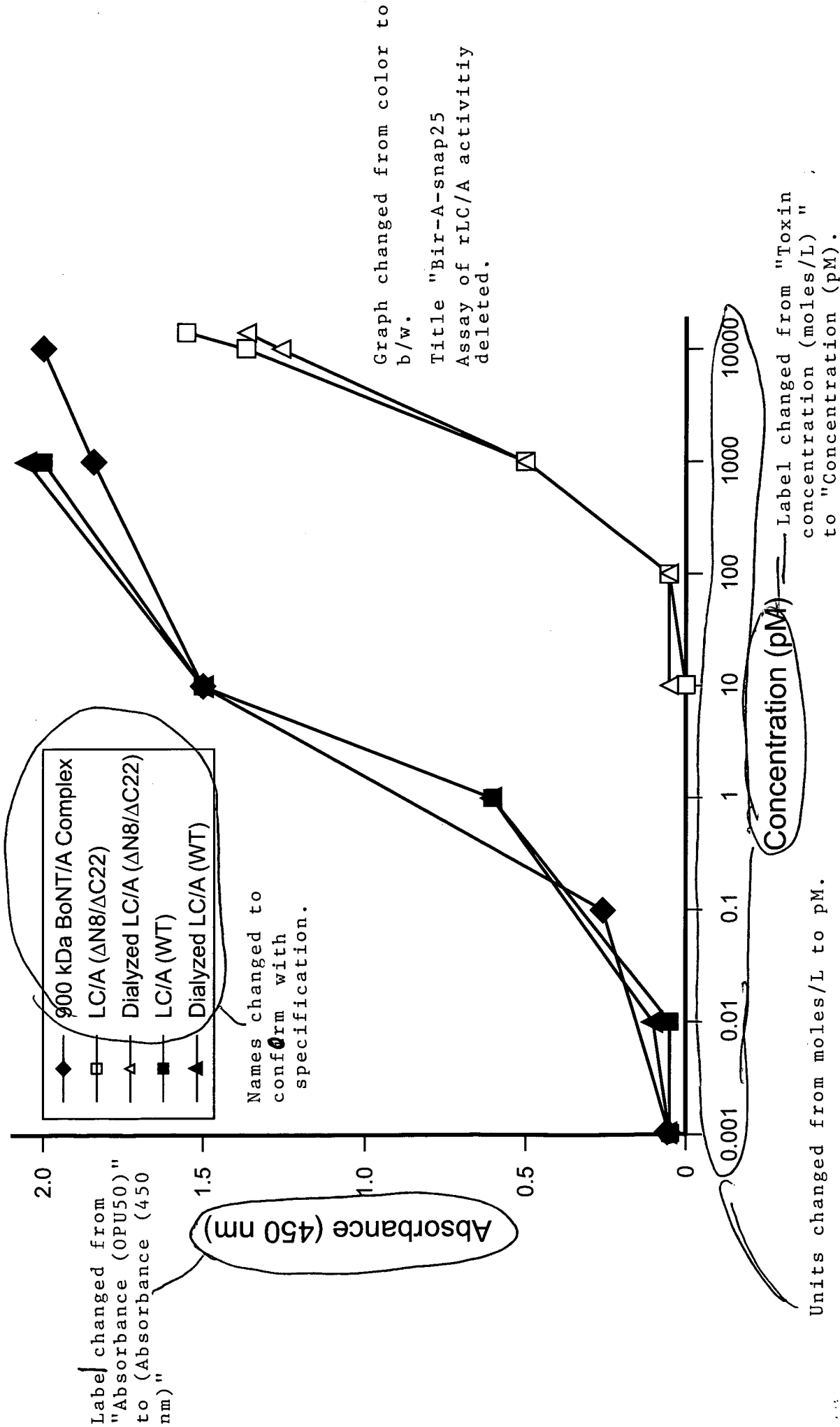


FIG. 10.

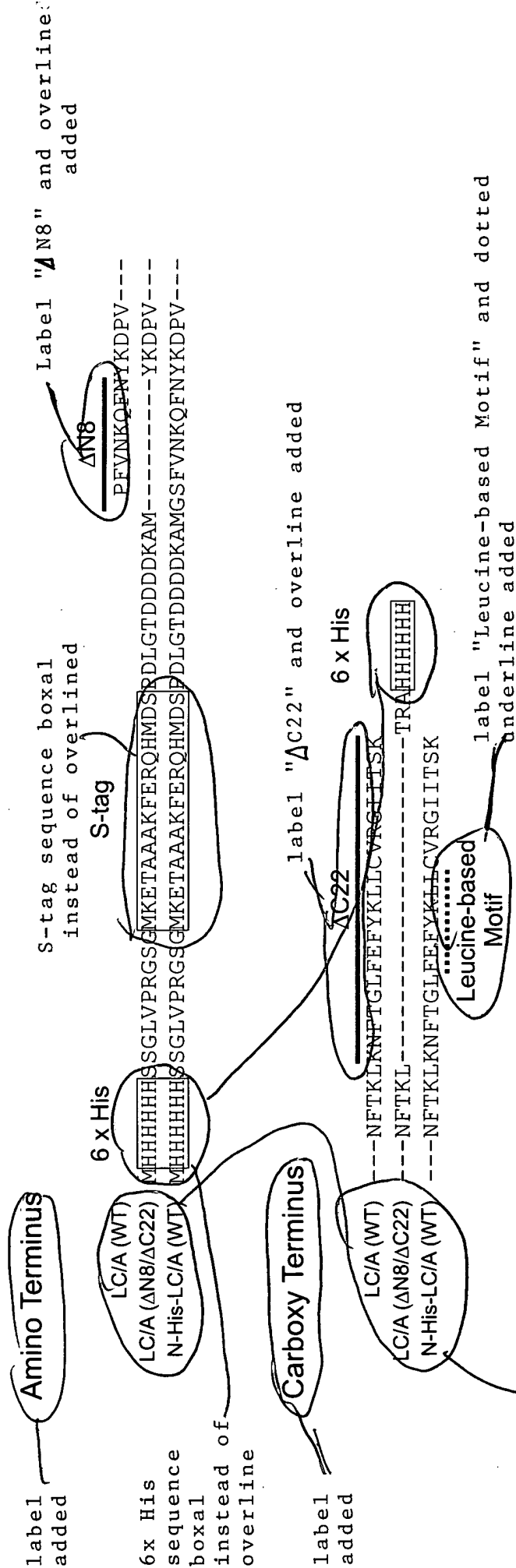


Figure changed from color to b/w

Title "Comparison of LC/A constructs expressed from E. coli for in vitro analysis" deleted.

Names changed to conform to specification
Wording referring to articles deleted

FIG. 11.

Label and outline added

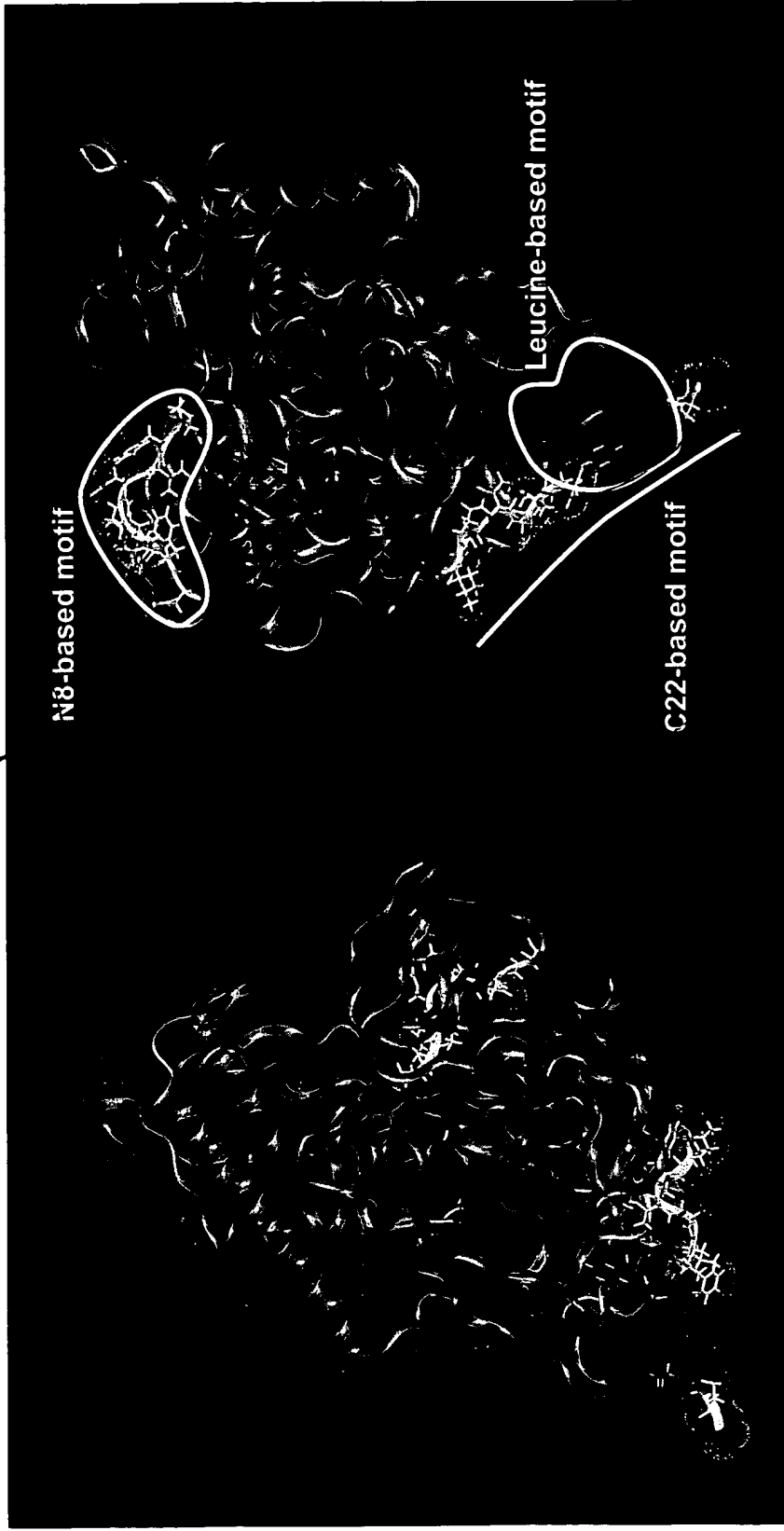


Image quality adjusted and size reduced
Image changed from color to b/w.

Label and outline added

FIG. 12.

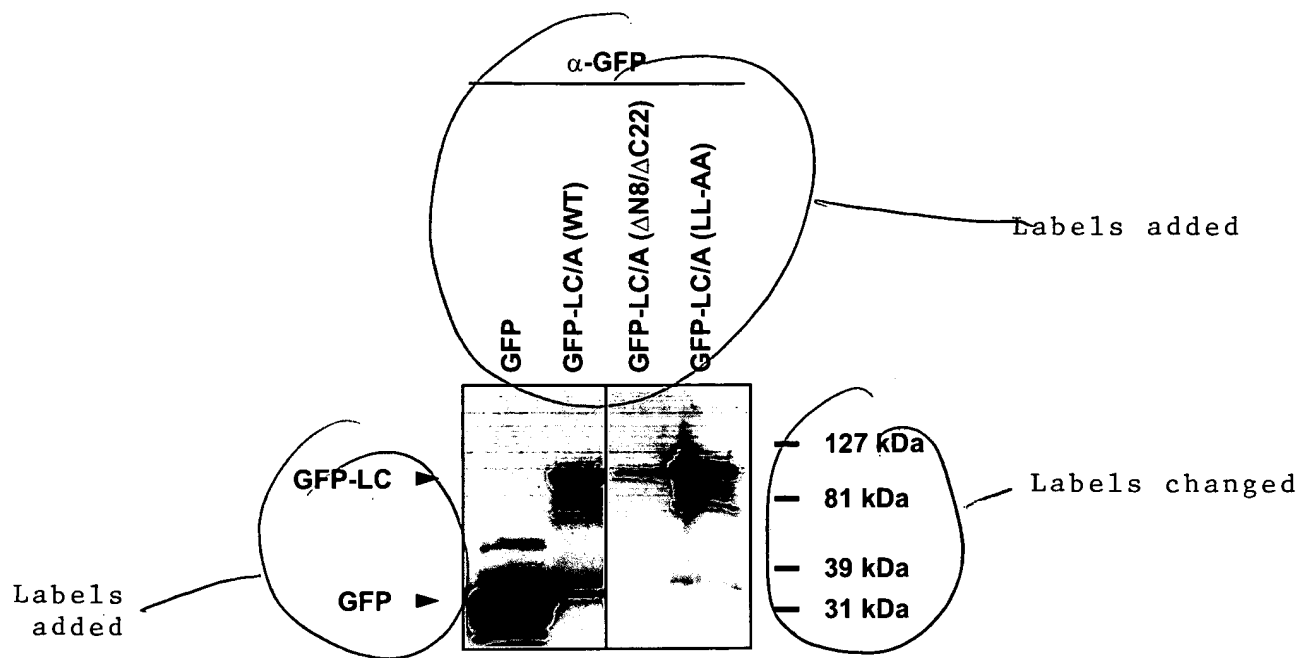


Image quality adjusted and size reduced
Original labels "G" "LC" "TA" and "AA" deleted.

FIG. 13.

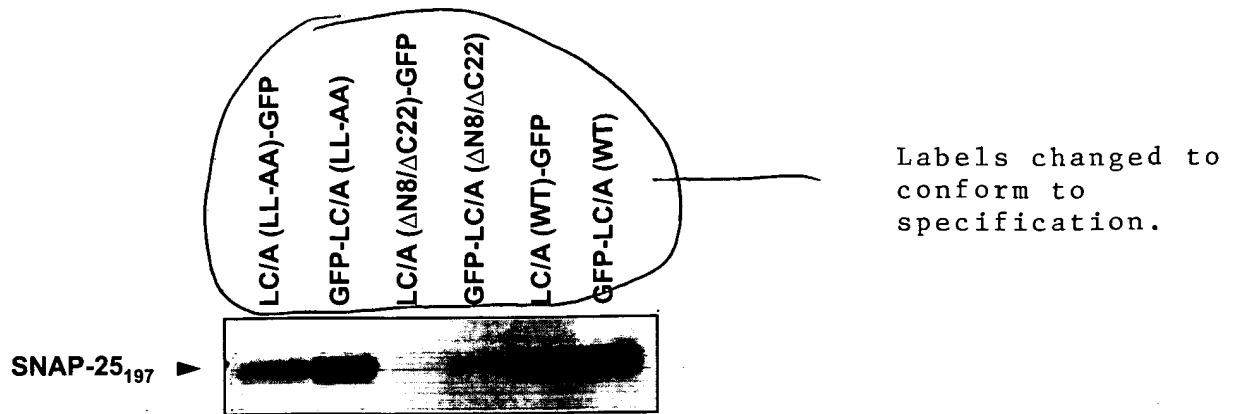


Image quality adjusted and size reduced.
Top 3 panels in original Fig. 13 deleted.

FIG. 14.

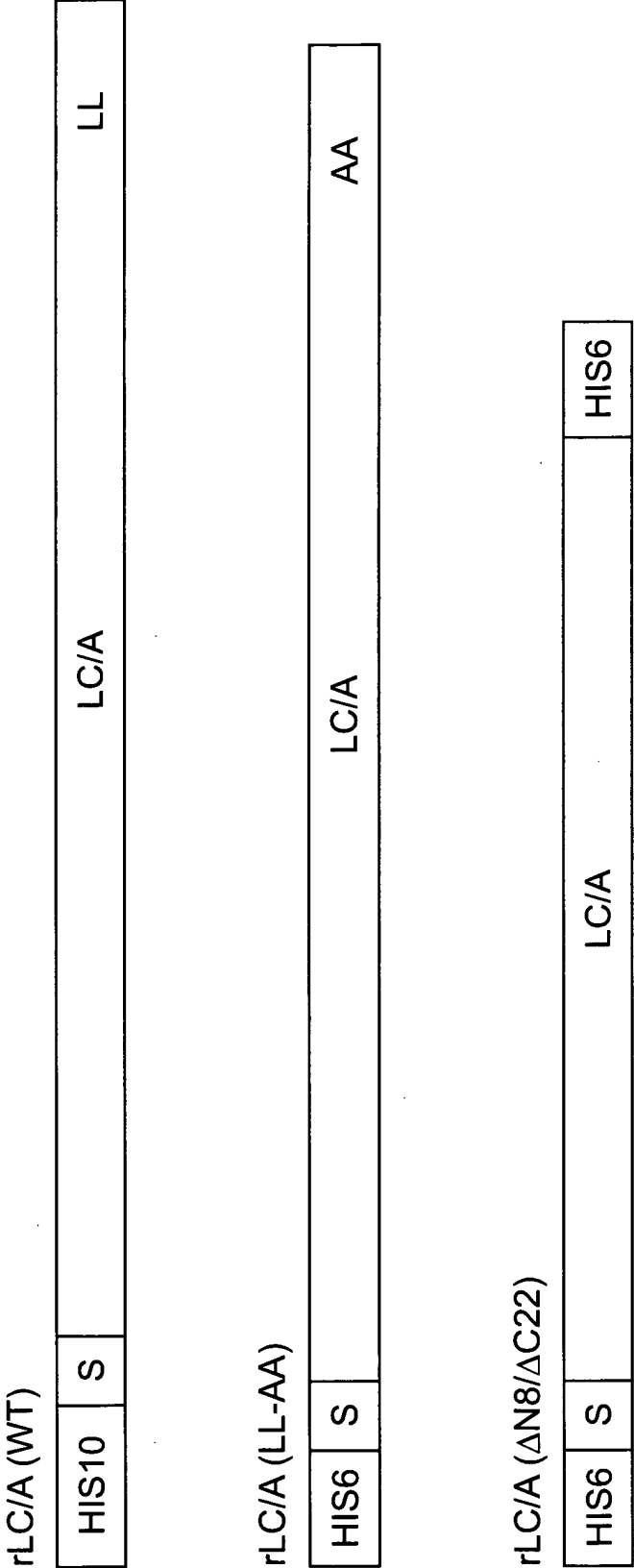
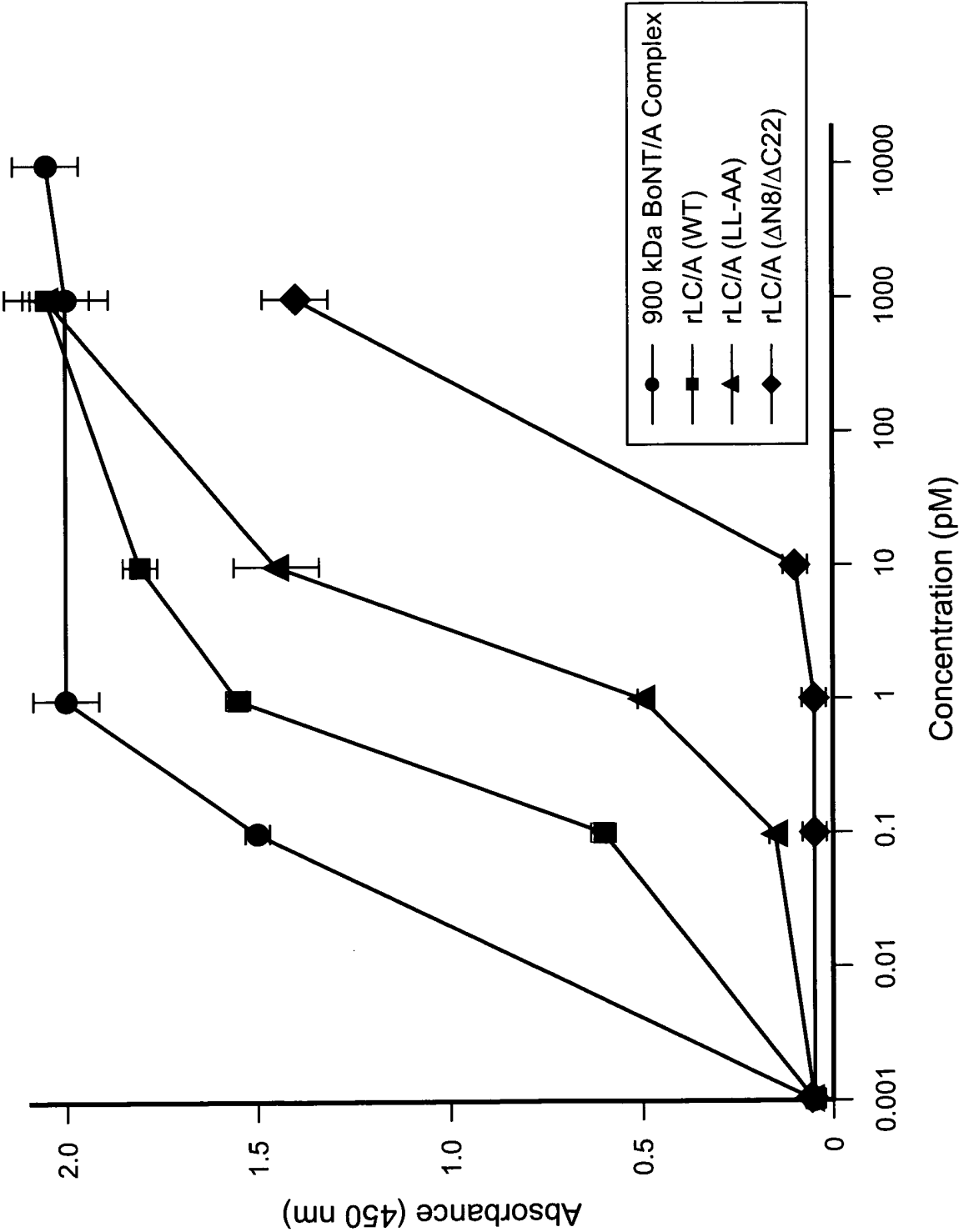


Figure changed to remove gray tones.

FIG. 15.



Graph re-drawn to enlarge

FIG. 16.

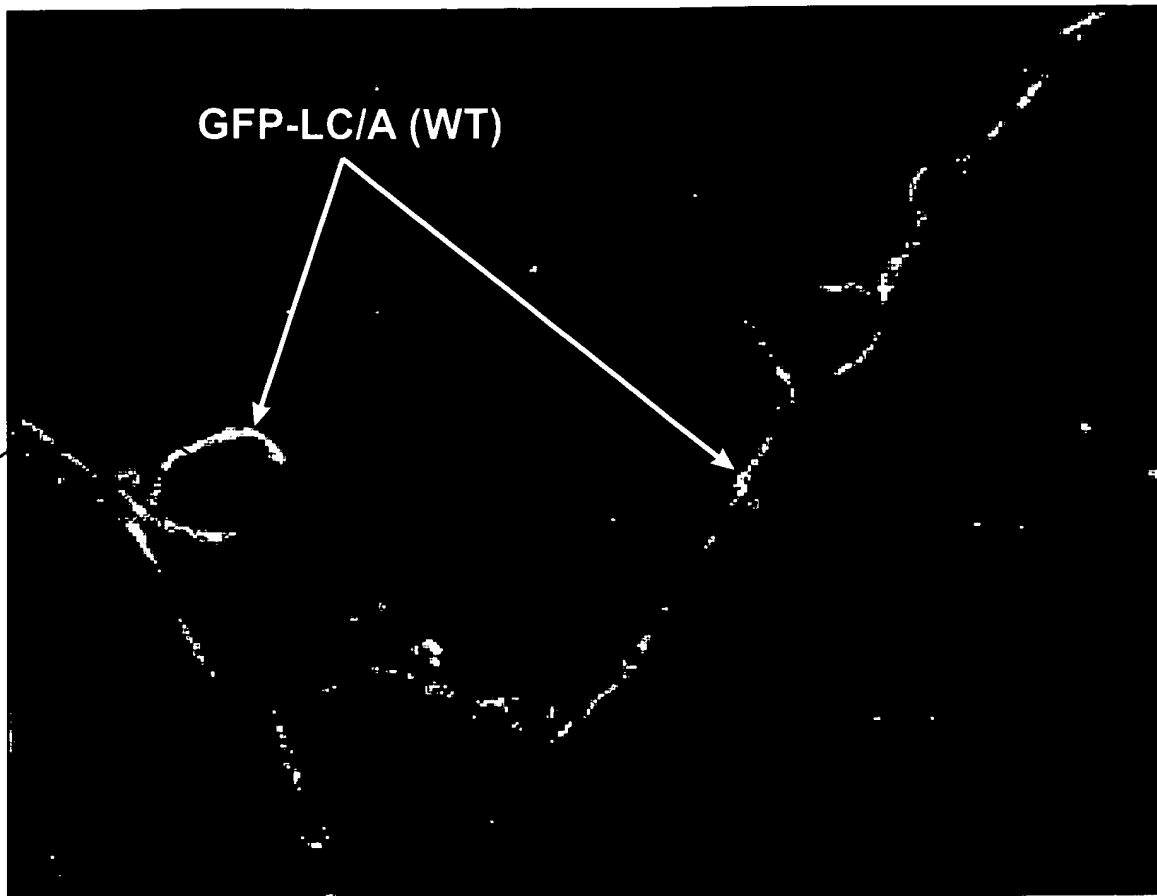
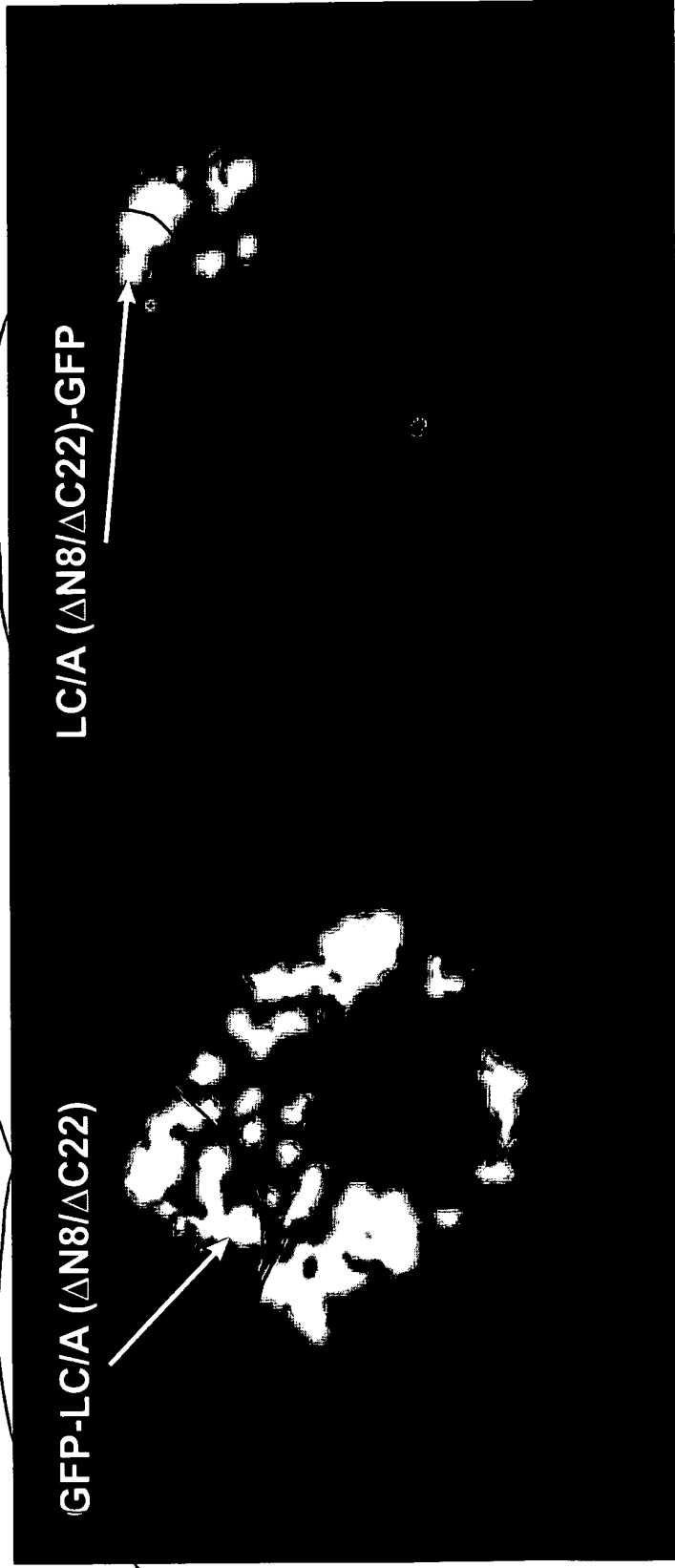


Image in left panel from original Fig. 16 deleted.
Image in right panel from original Fig. 16 had image quality
adjusted and image size enlarged.
Label "GFP-LC/A (WT)" and arrows added.

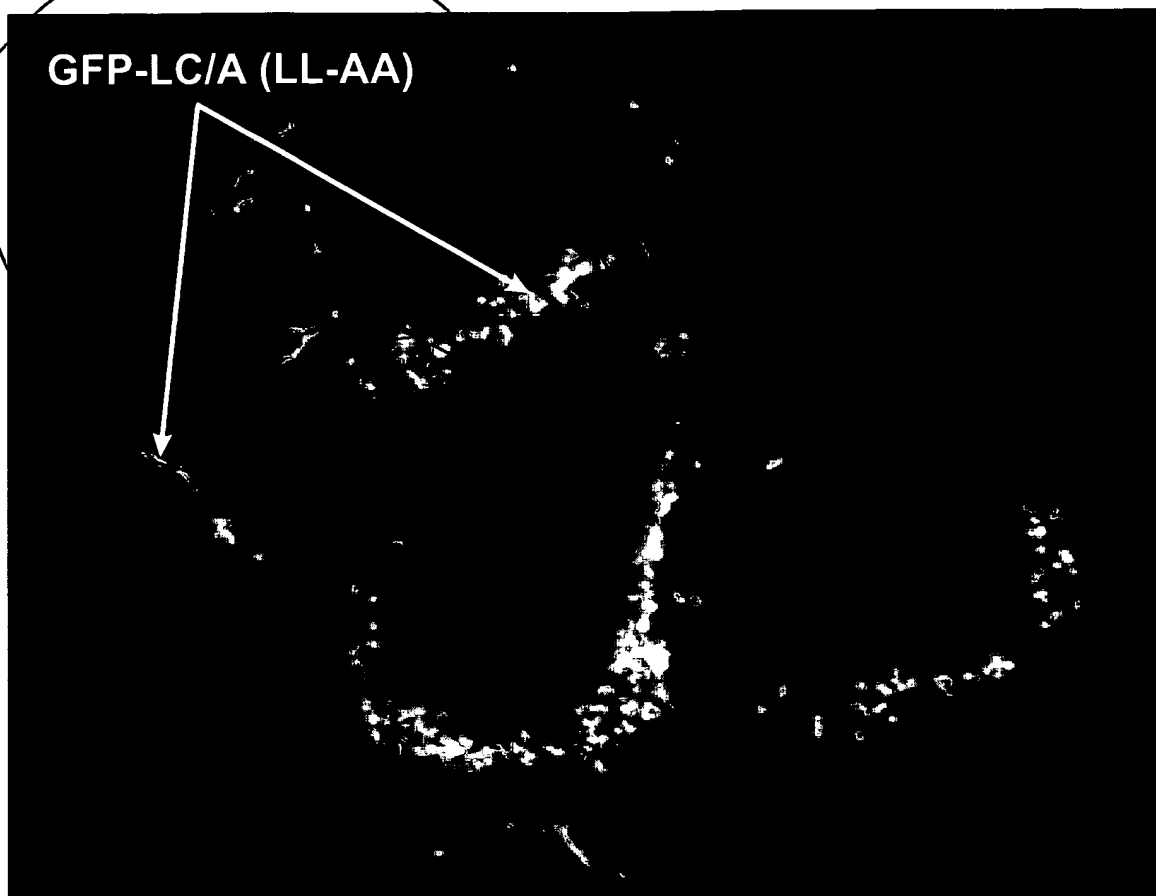
FIG. 17.



Labels and arrows added.

Image quality adjusted and image size enlarged.

FIG. 18.



The top left and bottom left panels from original Fig. 18 were deleted.

The right panel image from original Fig. 18 had image quality adjusted and size enlarged.

Label and arrows added.

FIG. 19.

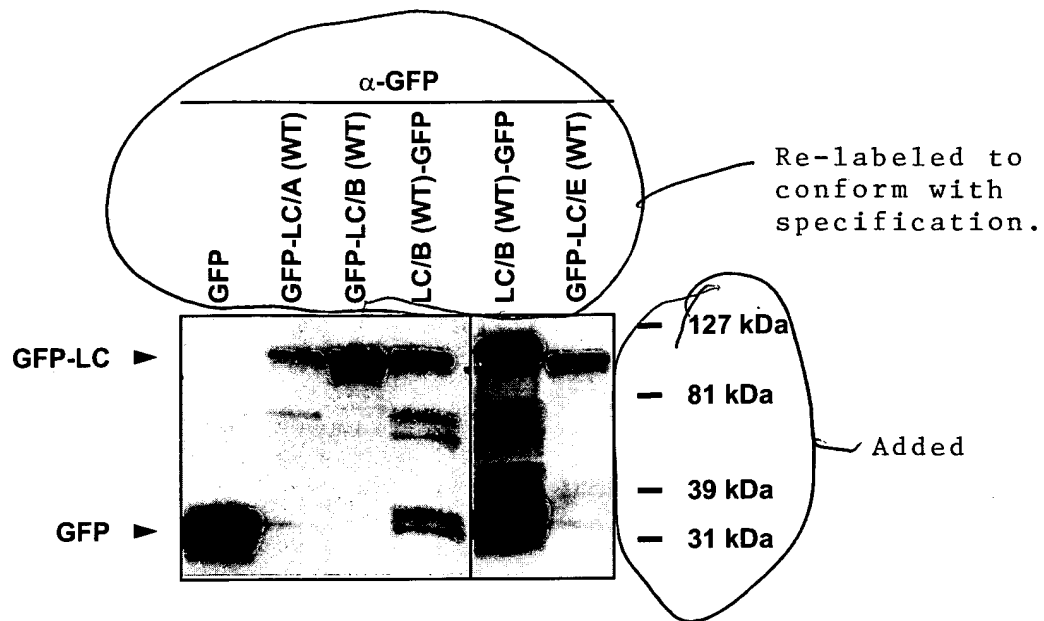


Image quality adjusted and image size reduced.

FIG. 20A.

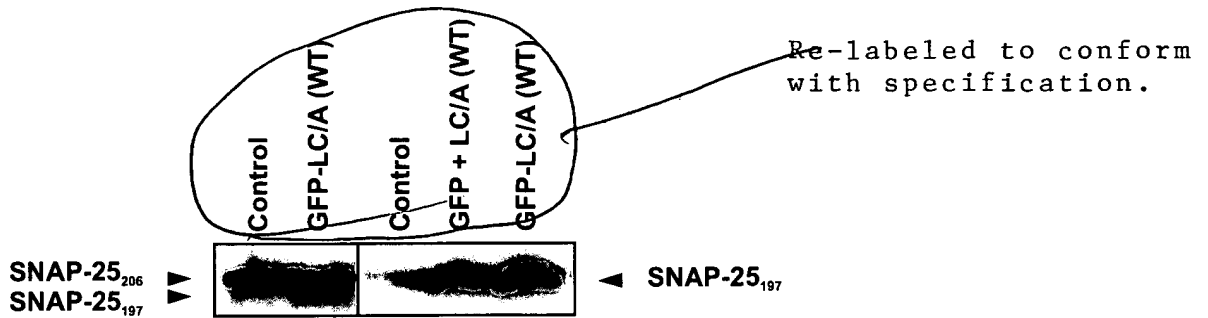


FIG. 20B.

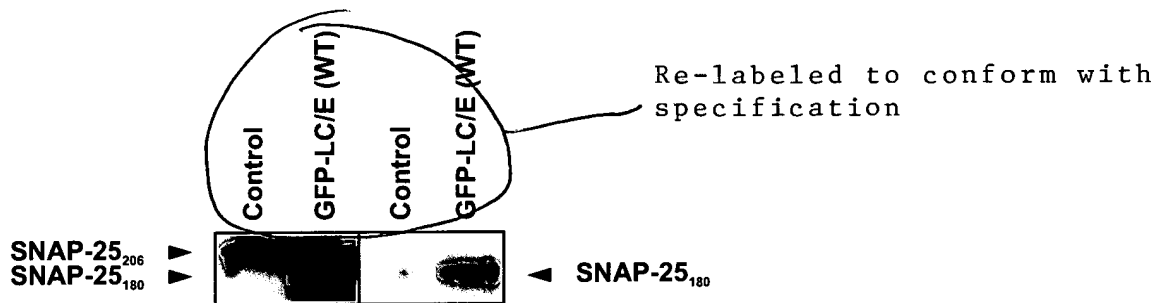


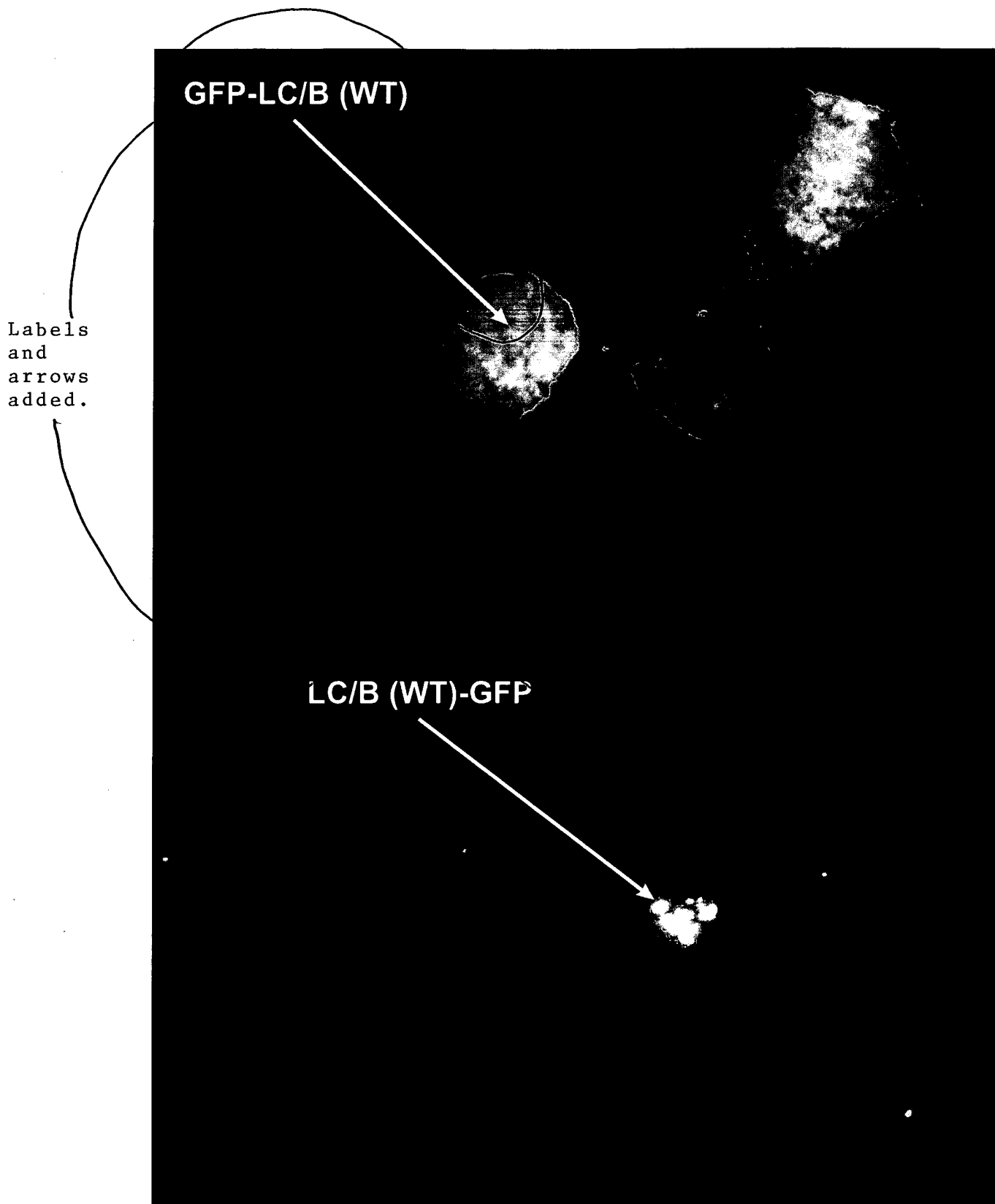
Figure divided into 20A and 20B.
Right top panel image from original Fig. 20 deleted.
Image quality adjusted and image size reduced.

FIG. 21.



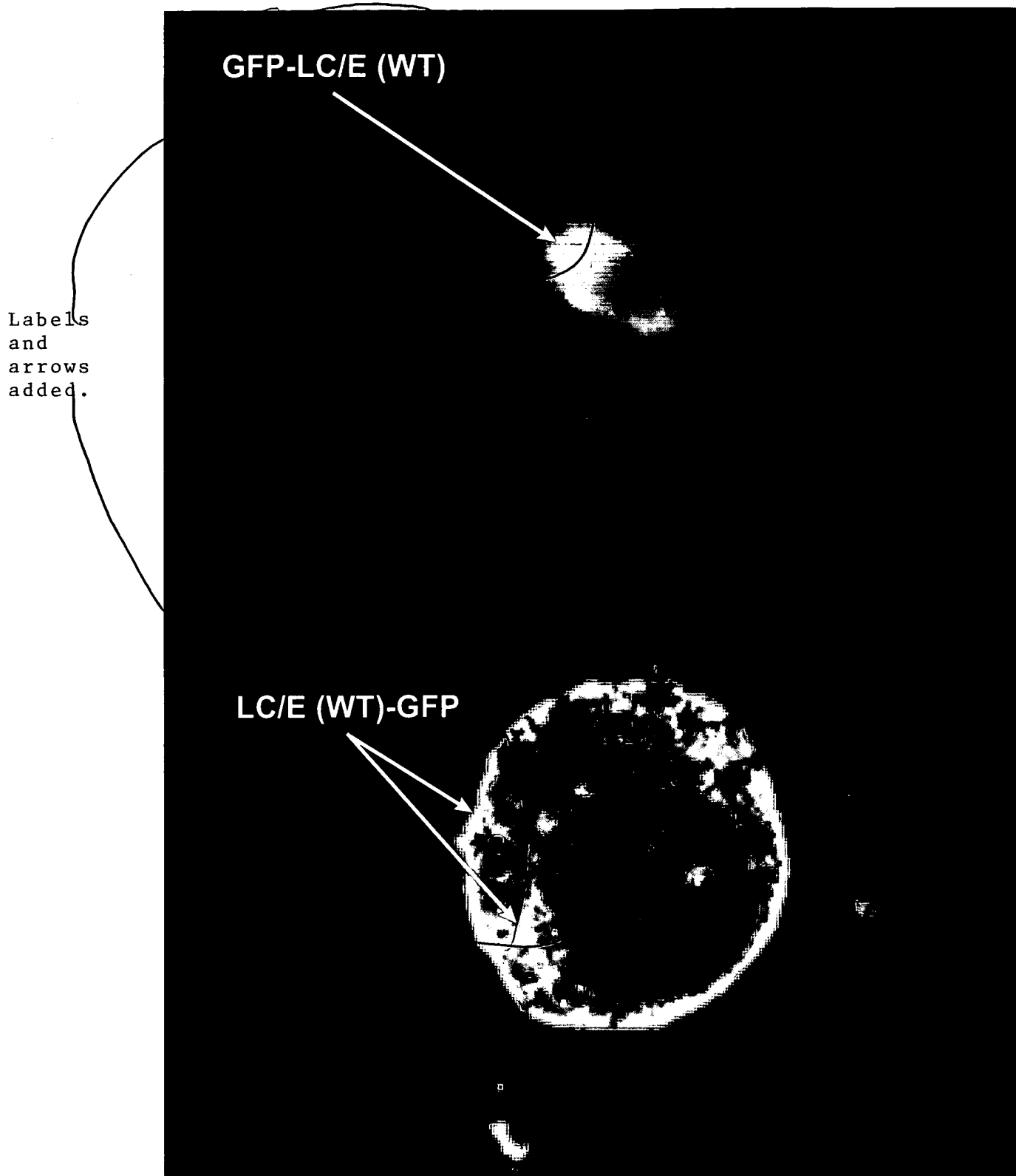
Labels and arrows added.
Image quality adjusted and image size enlarged.
Image orientation changed.

FIG. 22.



Bottom left and top right panel images from original Fig.22 deleted.
Top left and bottom right panel images from original Fig. 22 had
image quality adjusted and image size enlarged.

FIG. 23.



Only top left panel and right panel from original Fig 23 kept and other images were deleted. Image quality adjusted and image size enlarged.

FIG. 24A.

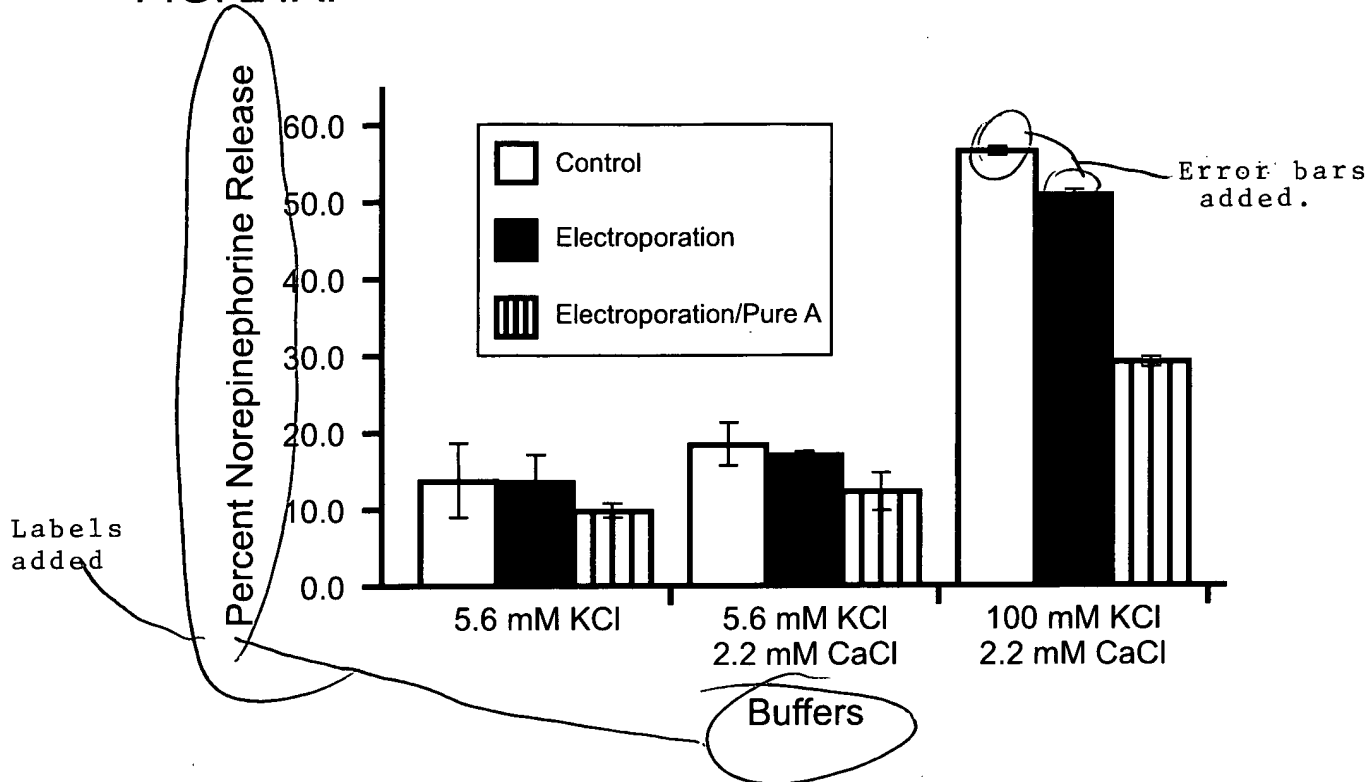
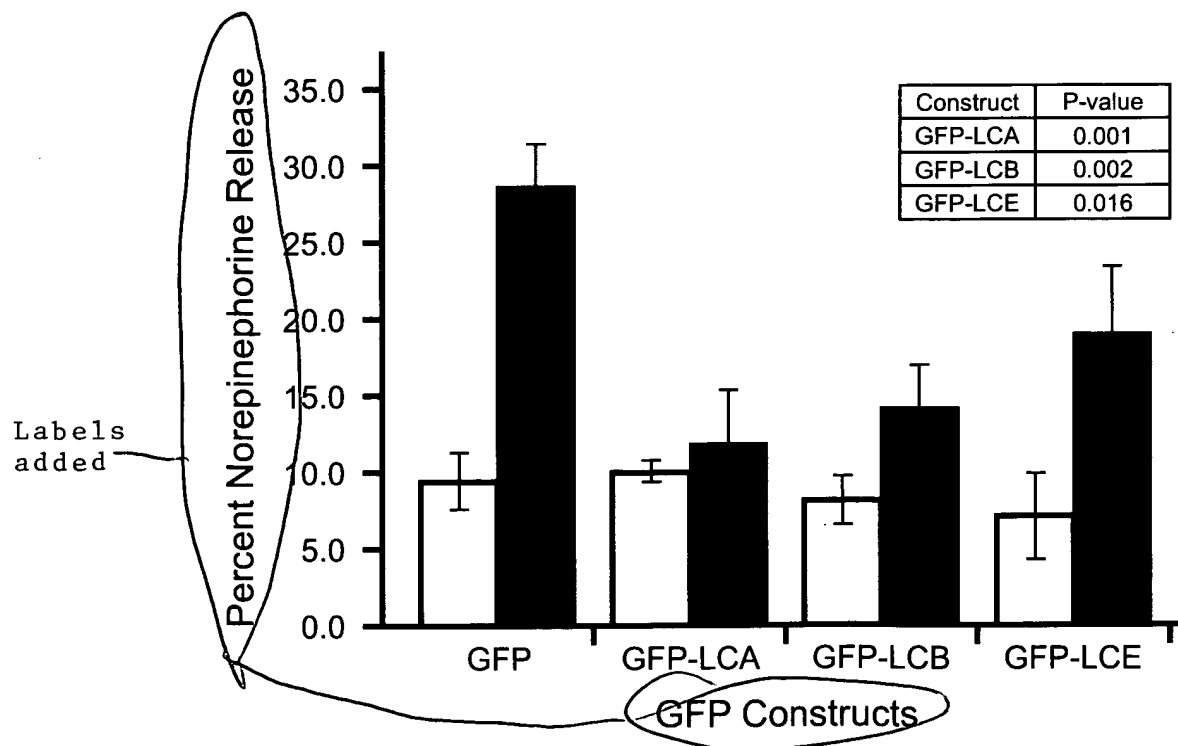


FIG. 24B.



Graphs re-drawn to remove grey-tones.

FIG. 25.

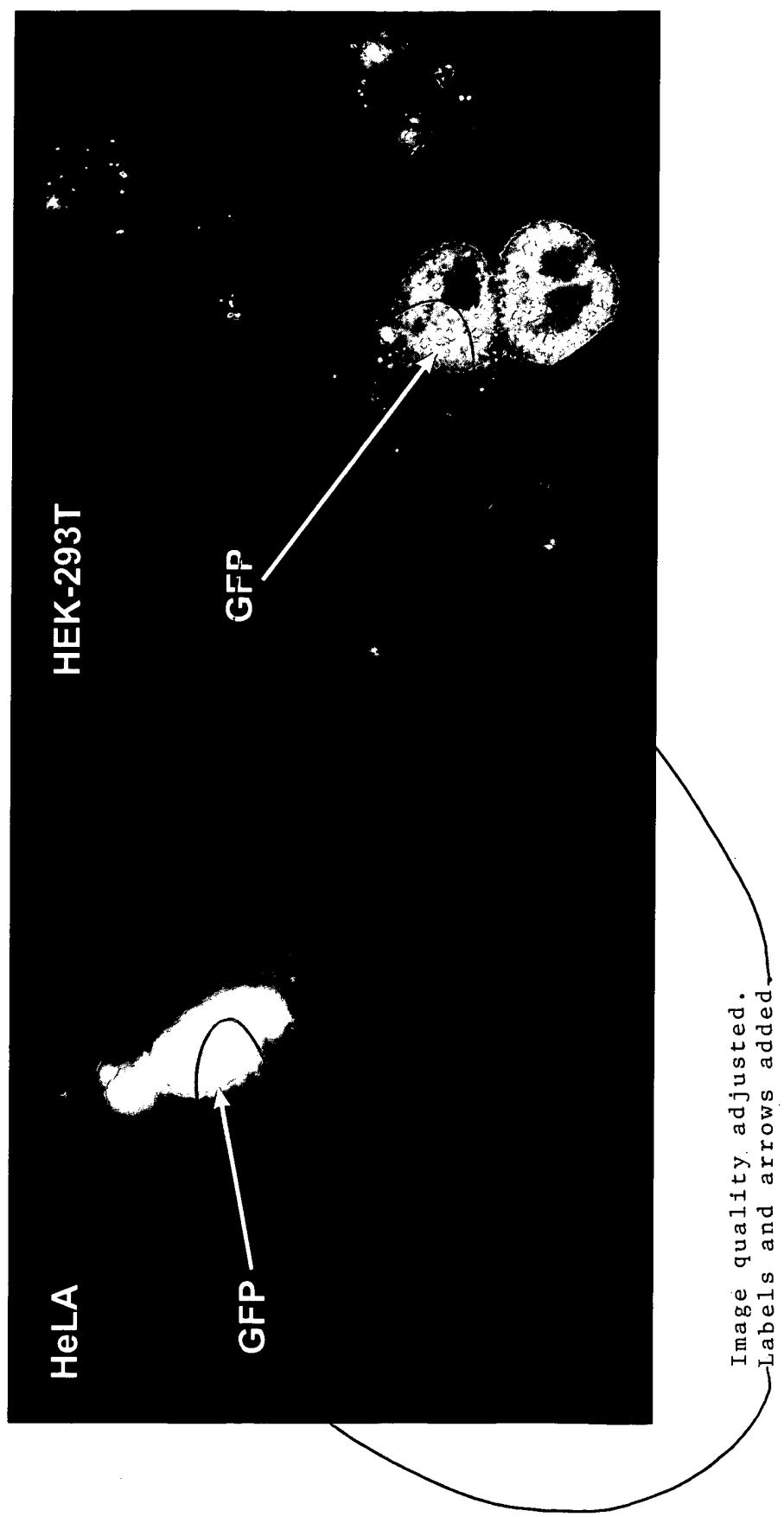


FIG. 26.

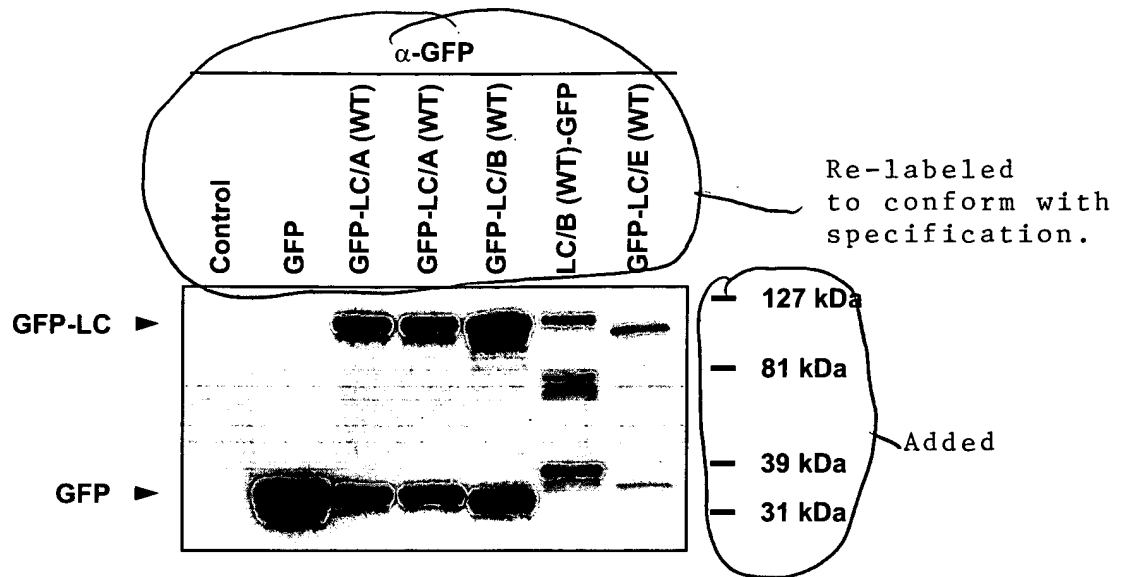


Image quality adjusted and image size reduced.
Bottom panel from original Fig. 26 deleted.

FIG. 27.



Top right panel from original FIG. 27 deleted.
Remaining panels had image quality adjusted and image size enlarged.
Labels and arrows added.

FIG. 28.

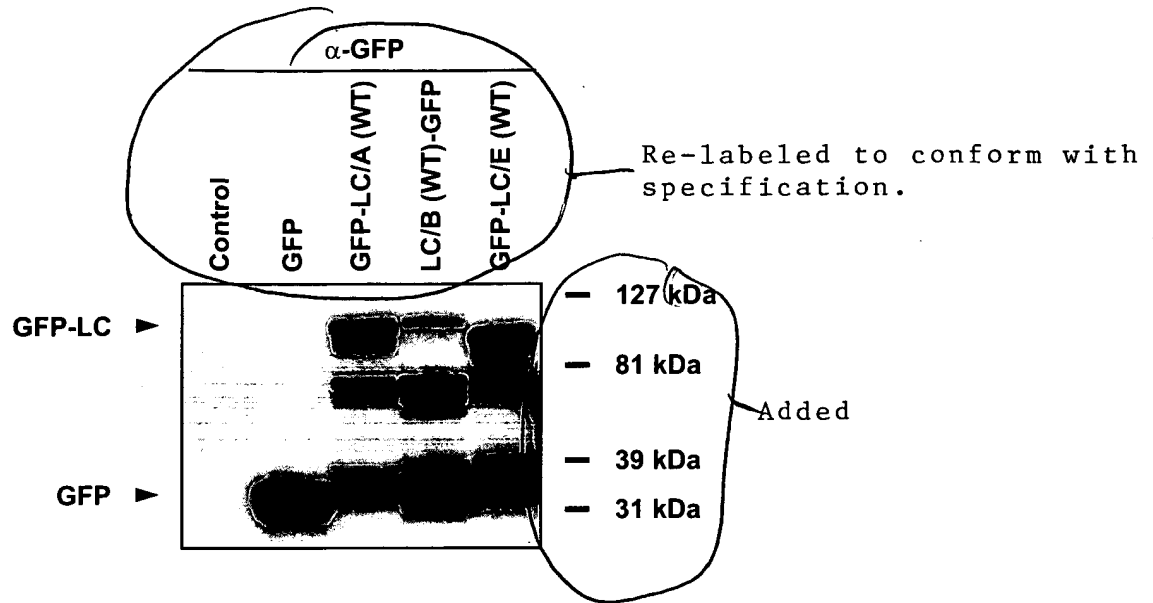
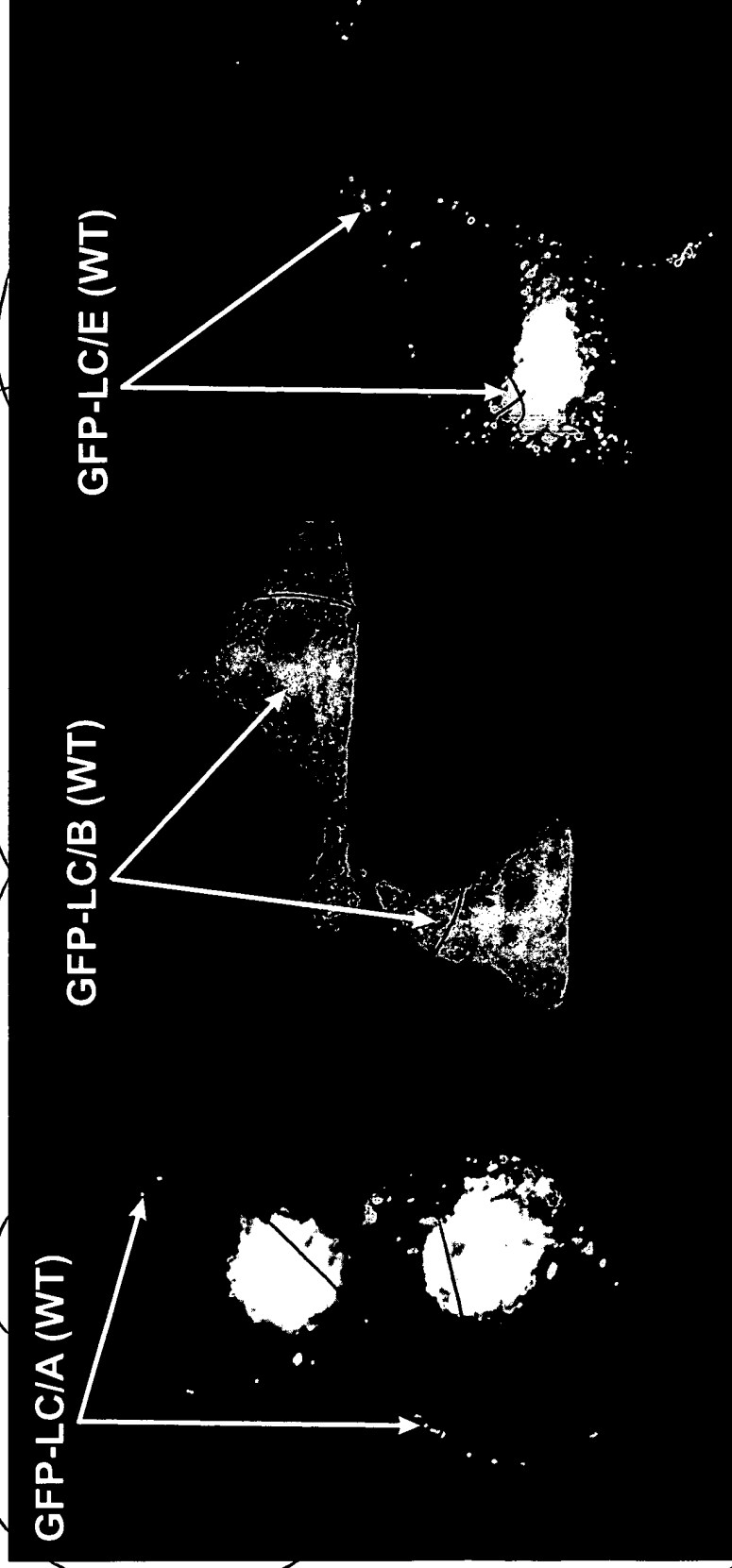


Image quality adjusted and size reduced.

FIG. 29.



Bottom right panel image from original Fig. 29 was deleted.
Remaining panels had image quality adjusted and image size enlarged.
Labels and arrows added.

FIG. 30A.

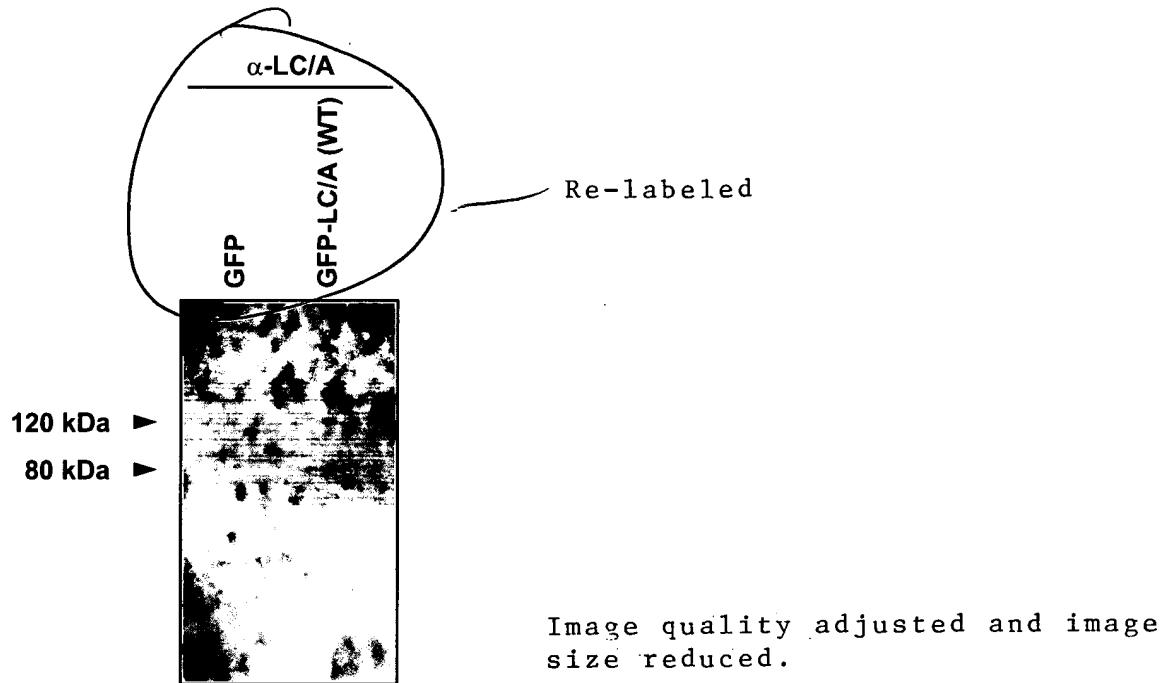


FIG. 30B.

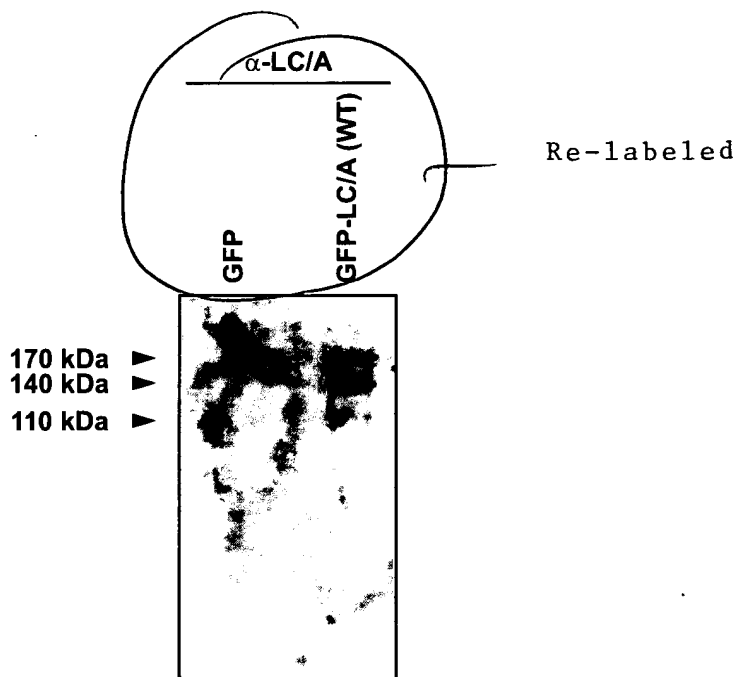


FIG. 31A.

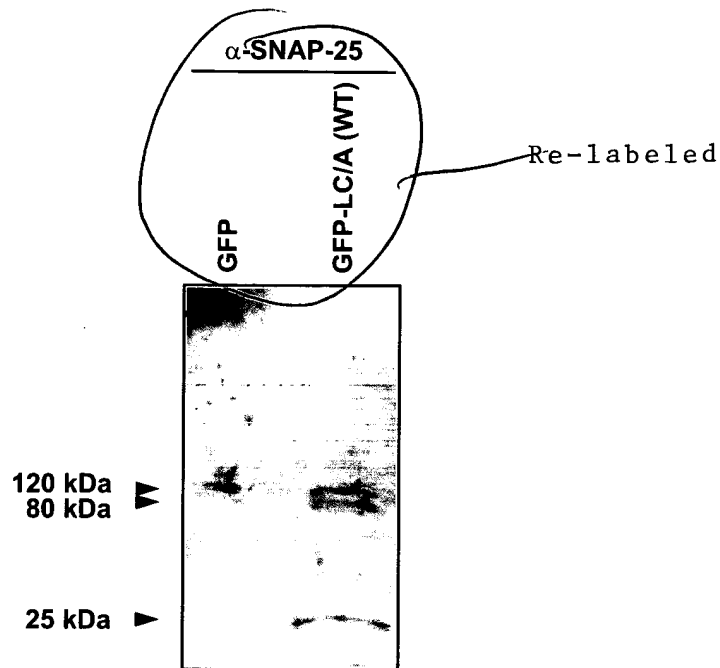


Image quality adjusted and image size reduced.

FIG. 31B.

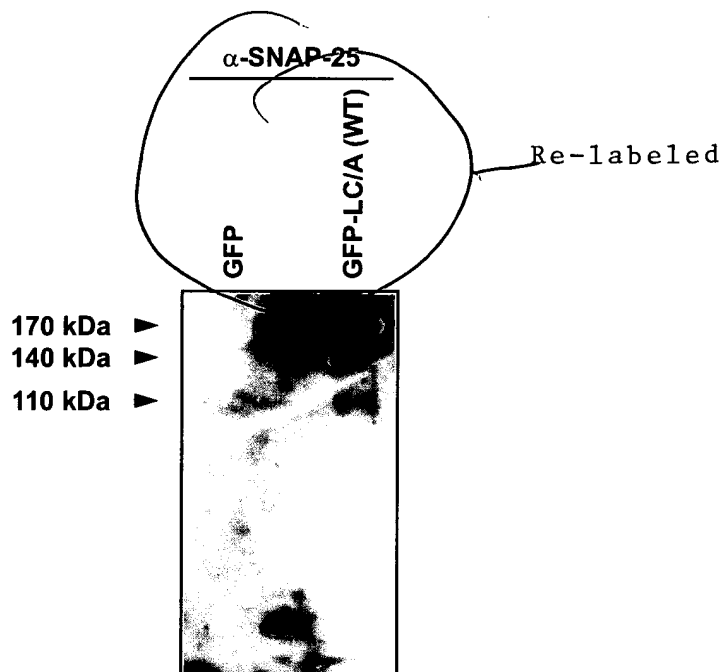
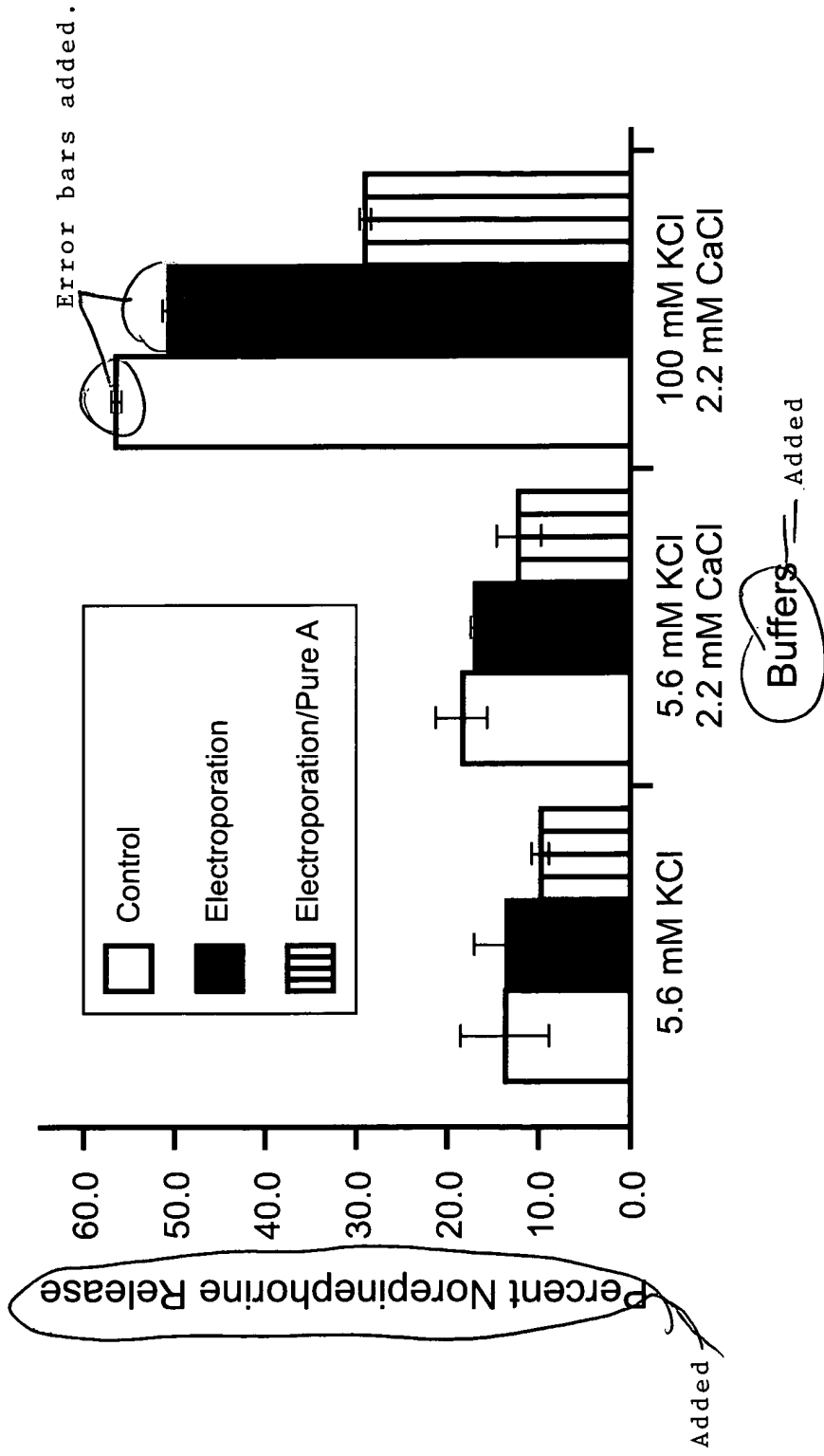


FIG. 32.



Graft re-drawn to eliminate half-tones.

FIG. 33.

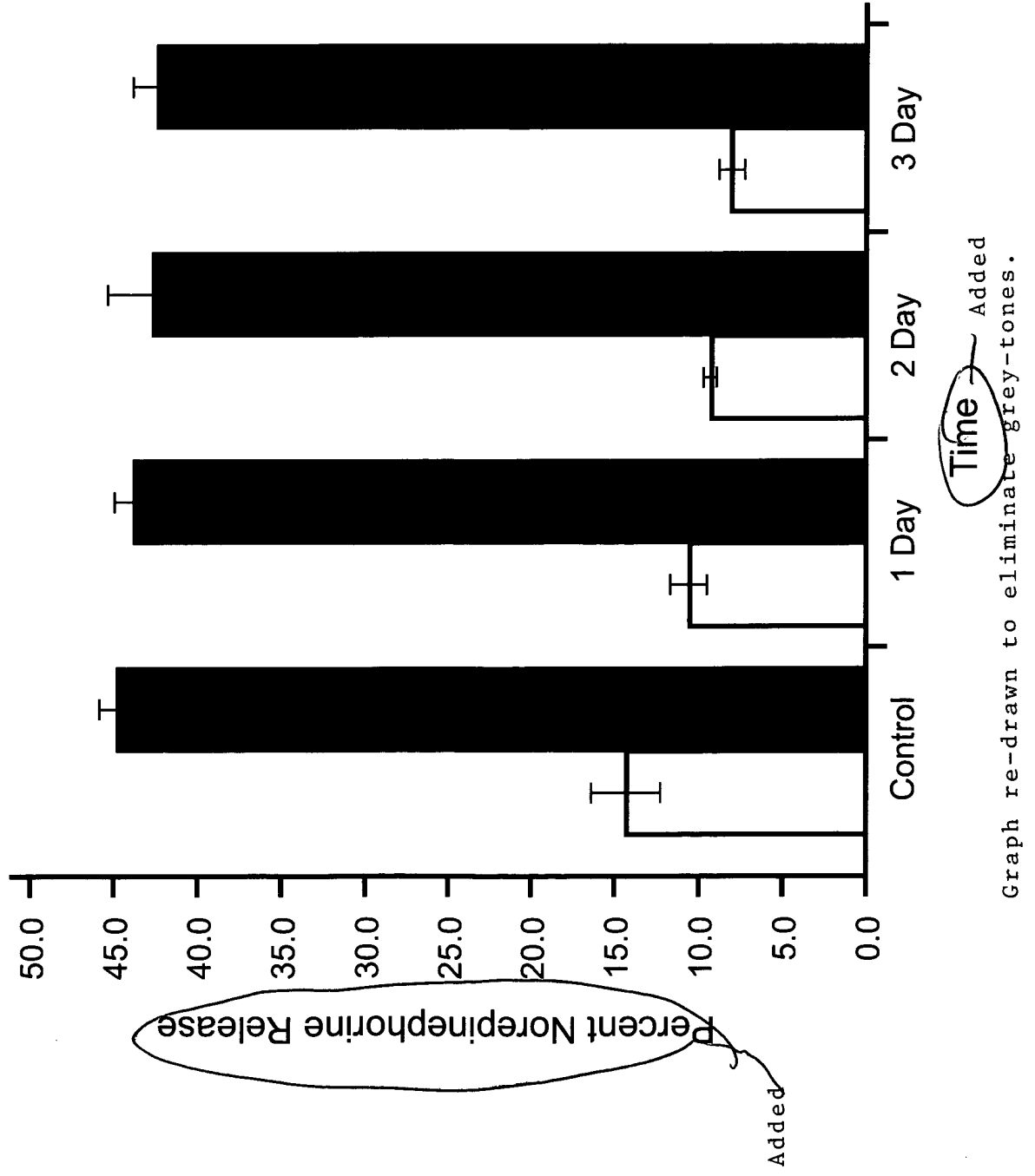


FIG. 34.

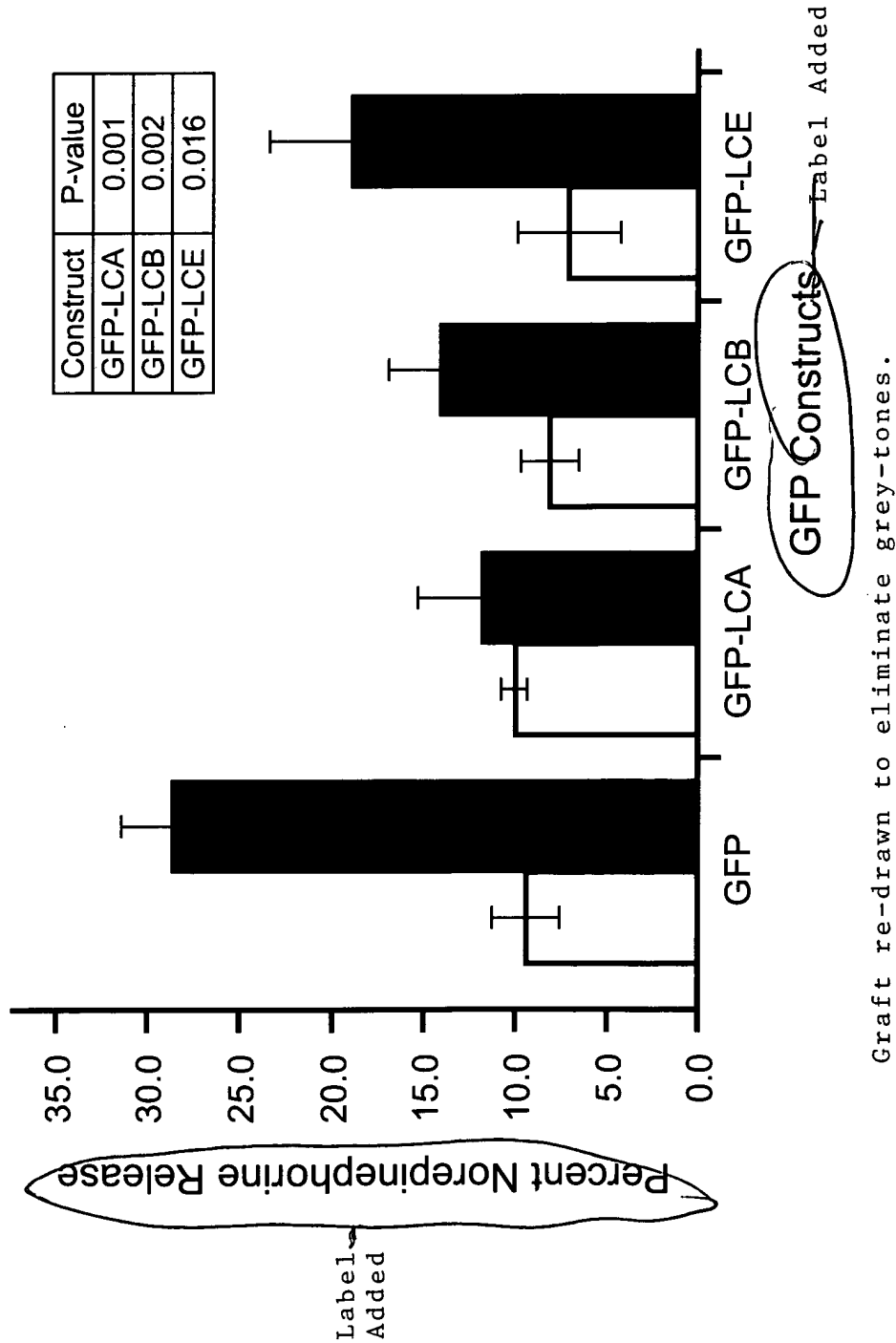
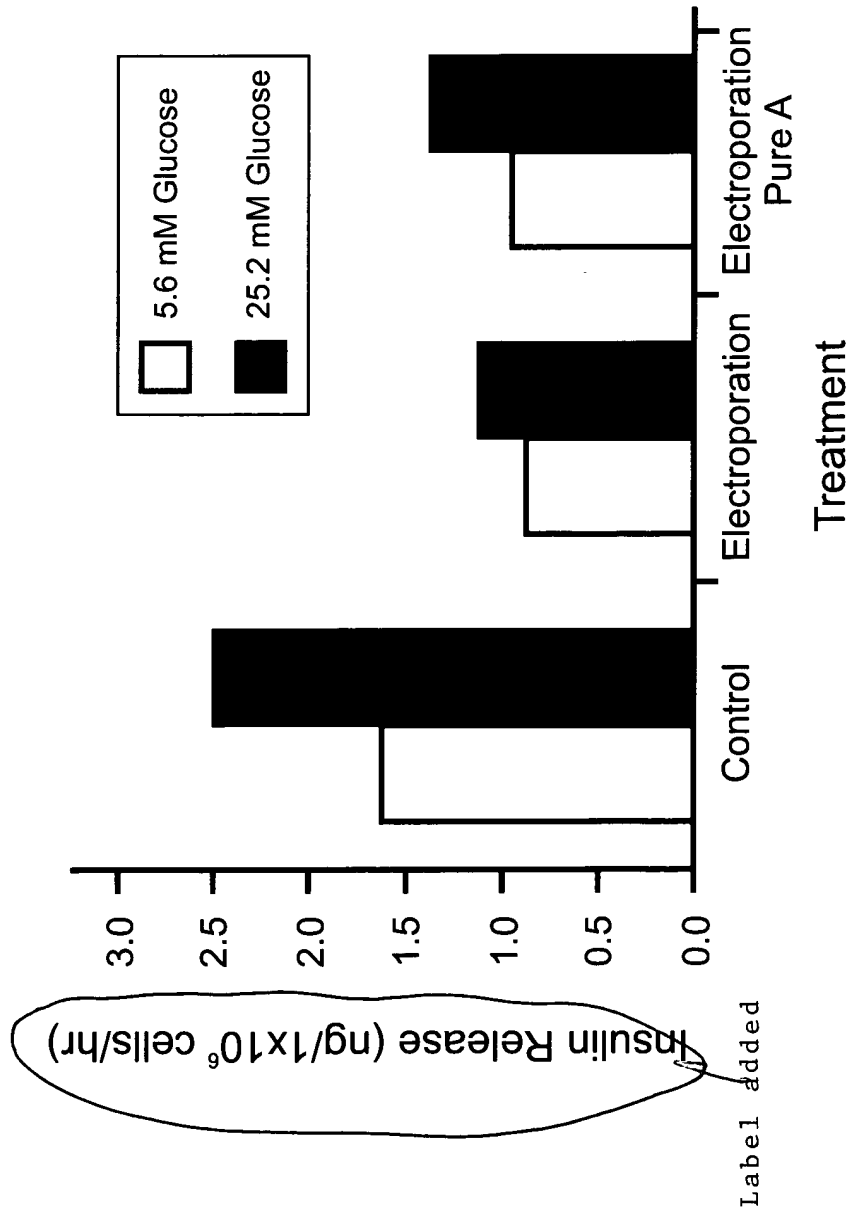


FIG. 35.



Graft re-drawn to eliminate grey-tones.

FIG. 36.

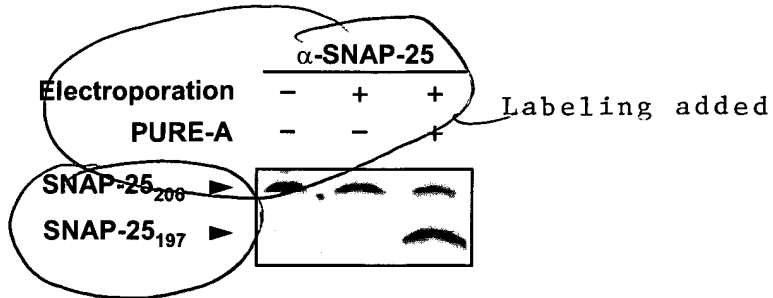
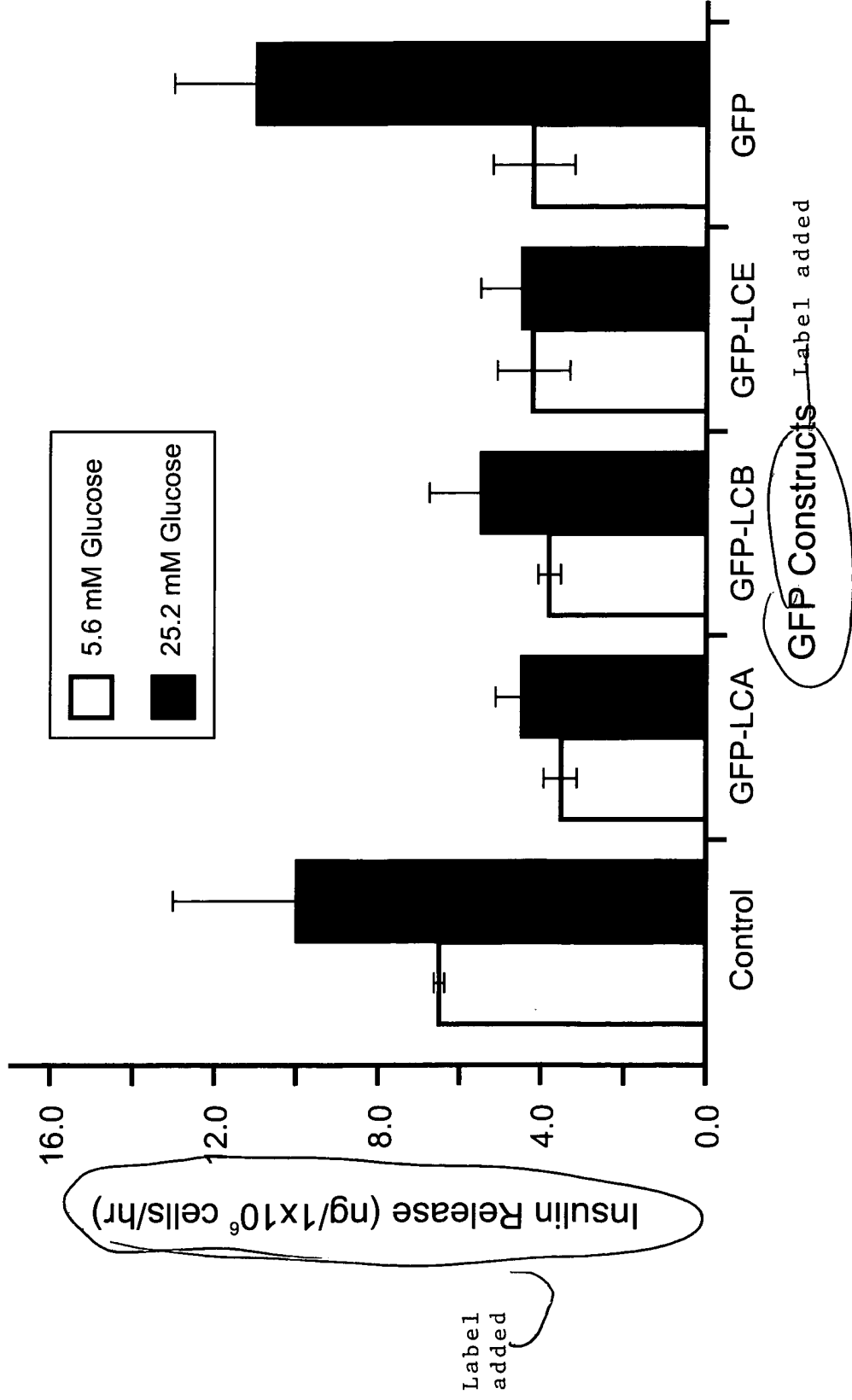


Image quality adjusted and image size reduced.

Image re-cropped to show uncleaved SNAP-25 bands.

FIG. 37.



Graft re-drawn to eliminate grey-tones.